

Organic Reactions

Organic Reactions

VOLUME V

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NEW YORK

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FIFTH PRINTING, AUGUST, 1962

PRINTED IN THE UNITED STATES OF AMERICA

PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of about twelve chapters, each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed.

Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters *and the entries in the tables, users of the books will be able to find information* desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically in volumes of about twelve chapters, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

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CHAPTER 1

THE SYNTHESIS OF ACETYLENES

THOMAS L. JACOBS

University of California

Los Angeles

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INTRODUCTION

Many advances have been made in recent years in the methods for the synthesis of acetylenes, and many of these compounds are now rather readily available in the pure state.

Acetylene was first prepared by Davy,¹ who treated potassium acetylide with water; propyne, the first substituted acetylene, was obtained in 1861 by the action of sodium ethoxide on bromopropene² or of ethanolic potassium hydroxide on propylene dibromide.³ At the present time alkynes are usually synthesized by the alkylation of sodium acetylide or substituted metallic acetylides, often in liquid ammonia,

¹ Davy, *Ann.*, 23, 144 (1837).

² Sawitsch, *Compt. rend.*, 52, 399 (1861); *Ann.*, 119, 185 (1861).

³ Morkownikoff, *Bull. soc. chim. France*, 14, 90 (1861); *Ann.*, 118, 332 (1861).

and 1-alkynes are also obtained in good yield by dehydrohalogenation of suitable halides with sodium amide or in certain cases by ethanolic alkali.

The present discussion will be limited to methods for the creation of a carbon-carbon triple bond and to the alkylation of metallic acetylides. No attempt will be made to deal with the multitude of processes in which sodium or other metallic derivatives of acetylenes or acetylene-magnesium bromide react with carbonyl compounds with the formation of products containing triple bonds. Neither will the closely related base-catalyzed condensations of acetylene or monosubstituted acetylenes with ketones to produce carbinols, the formation of diacetylenes by oxidation of metallic acetylides, or the replacement of the acetylenic hydrogen by halogen by the action of hypohalite be discussed.

THE SYNTHESIS OF ACETYLENES BY DEHYDROHALOGENATION

Dehydrohalogenation produces acetylenic compounds from dichlorides or dibromides of olefins, chloro- or bromo-olefins, and the mono- or di-chloro compounds prepared from aldehydes or ketones. Potassium hydroxide and sodium amide are employed most commonly to effect the reaction, although sodium hydroxide, alkali metal alkoxides, alkaline-earth carbonates or hydroxides, and amines have found occasional use. Alcoholic potassium hydroxide is now seldom employed in the aliphatic series because of the tendency of the triple bond to migrate away from the end of the chain under its influence, but aromatic acetylenes are still prepared conveniently by its use, often in higher yield than with sodium amide. Sodium amide causes the rearrangement of the triple bond to the 1-position because the insoluble sodium alkynide is formed; excellent yields of 1-alkynes are realized using this reagent. Aliphatic α,β -acetylenic acids can seldom be prepared by dehydrohalogenation because alkoxy acids, ketones, or polymers are the principal products. Mild conditions must be employed with arylpropionic acids to avoid decarboxylation.

Potassium Hydroxide

Alcoholic, usually ethanolic, potassium hydroxide has been the most widely used reagent for the synthesis of acetylenes, but no critical study of optimum conditions for the reaction has been made. Bromides react more readily than chlorides, and the formation of a bromoethylene from a dibromide occurs more easily than the preparation of an acetylene from the bromoethylene, so that it is sometimes advantageous with sensitive dibromides to remove the first molecule of hydrogen bromide

in the cold with dilute ethanolic alkali or other bases. With aliphatic compounds it is sometimes necessary to use sealed tubes or autoclaves and temperatures near 170° , but extended refluxing is usually sufficient with aryl chloro- or bromo-ethylenes. The reaction is more rapid at high concentrations of alkali, and excess alkali is usually employed. Ethanolic potassium hydroxide saturated at room temperature is about 4 *N* (around 20%), but solutions of more than twice this strength can be prepared by saturation at the boiling point. Some workers⁴ specify equal weights of ethanol and alkali, and recent directions⁵ for tolan call for 90 g. of potassium hydroxide in 150 ml. of ethanol, but in most reports the concentration is not given. Powdered potassium hydroxide moistened with ethanol is satisfactory for the preparation of *tert*-butylacetylene from the halides derived from pinacolone.⁶ With some compounds high concentrations give decreased yields, as illustrated by the dehydrohalogenation of the acetal of 2,3-dibromopropanal to propargyl acetal.⁷ Ordinary 95% ethanol is often satisfactory although absolute ethanol is sometimes specified. Water is always present since it is a product of the reaction and since commercially available potassium hydroxide contains about 86% alkali along with some potassium carbonate and considerable water. The reaction time varies widely. Thus, 1-bromo-1-furylethylene gives a maximum yield (25%) of furylacetylene on heating for three minutes at 100° with a slight excess of 18% ethanolic potassium hydroxide,⁸ but stilbene dibromide gives tolan in good yield and free from bromo compound only after twenty-four hours' refluxing with a 40% solution.⁵

Other solvents have been used. The yield of acetylenedicarboxylic acid from α,β -dibromosuccinic acid is higher with *methanolic* than with ethanolic potassium hydroxide.⁹ A methanol solution saturated at room temperature is about 6 *N*. It darkens less rapidly than an ethanol solution but has a lower boiling point. *Butyl alcohol* was used by Tapley and Giesey¹⁰ as the solvent in the dehydrohalogenation of propylene dibromide, and many workers have adopted this procedure for propyne. It has been used occasionally for other acetylenes.^{10c} *Diethylene glycol*

⁴ Johnson and McEwen, *J. Am. Chem. Soc.*, **48**, 463 (1926).

⁵ Smith and Falkof, *Org. Syntheses*, **22**, 50 (1942).

⁶ (a) Ivitsky, *Bull. soc. chim. France*, [4] **35**, 357 (1924); (b) Gray and Marvel, *J. Am. Chem. Soc.*, **47**, 2795 (1925).

⁷ Gard, *Ann. chim.*, [10] **13**, 336 (1930).

⁸ Moureu, Dufraisse, and Johnson, *Ann. chim.*, [10] **7**, 14 (1927).

⁹ Abbott, Arnold, and Thompson, *Org. Syntheses*, **18**, 3 (1935); *Coll. Vol.* **2**, 10 (1943).

¹⁰ (a) Tapley and Giesey, *J. Am. Pharm. Assoc.*, **15**, 115 (1926); (b) Heisig and Davis, *J. Am. Chem. Soc.*, **57**, 339 (1935); (c) Cleveland and Murray, *J. Chem. Phys.*, **11**, 450 (1943).

has been employed in the synthesis of propyne,¹¹ but no record of the preparation of other acetylenes in this solvent has been found. Ethylene glycol has been used as the solvent in the synthesis of methyl propargyl ether.¹² A 5% solution of potassium hydroxide in Cellosolve (the monoethyl ether of ethylene glycol) is very effective for the dehydrochlorination of polyvinyl chloride,¹³ and such a solution is superior to ethanolic alkali for converting 1-bromo-1-methylcyclobutane to methylcyclobutene.¹⁴ Potassium hydroxide in pyridine has been used to prepare β -naphthylphenylacetylene from the corresponding chloroethylene,¹⁵ for neither methanolic nor molten alkali is effective. Aqueous alkali is sometimes preferable to ethanolic for dehydrohalogenation of halogenated acids,¹⁶ as in the preparation of phenylacetylenephosphonic acid,^{16a} 4,4'-dinitrotolan-2,2'-disulfonic acid,^{16b} 5-bromo-2-furylpropionic acid,^{16c} and several substituted phenylpropionic acids.^{16d}

Dehydrohalogenation by distillation at partially reduced pressure from solid potassium hydroxide was first used by Krafft and Reuter¹⁷ to prepare higher 1-alkynes from dibromides or bromoethylenes. Rapid distillation at low pressures gave mainly bromoolefins. It was claimed that no rearrangement occurred, although no critical study was made. The method has been applied successfully to the preparation of the sensitive acetylenic ethers from alkoxy- or aryloxy-bromoethylenes.¹⁸ However, 1,2,3-tribromopropane gives 2,3-dibromopropene but almost no propargyl bromide¹⁹ by distillation from solid sodium hydroxide or potassium hydroxide at atmospheric pressure.

Molten potassium hydroxide is a reagent which has found fairly wide application.¹⁷ Phenylacetylene is most simply prepared by dropping ω -bromostyrene onto the molten alkali at 200–220°.²⁰ Pure potassium hydroxide melts at 360°,²¹ but the monohydrate melts at 143°,²² and the

¹¹ (a) Yost, Osborne, and Garner, *J. Am. Chem. Soc.*, **63**, 3492 (1941); (b) Skei, Ph.D. Thesis, University of California at Los Angeles, 1942, p. 121.

¹² Hedbron, Jones, and Lacey, *J. Chem. Soc.*, **1946**, 27.

¹³ Marvel, Sample, and Roy, *J. Am. Chem. Soc.*, **61**, 3241 (1939).

¹⁴ Shand, Schomaker, and Fischer, *J. Am. Chem. Soc.*, **66**, 630 (1944).

¹⁵ Ruggli and Reinert, *Helv. Chim. Acta*, **9**, 67 (1926).

¹⁶ (a) Bergmann and Bondi, *Ber.*, **66**, 278 (1933); (b) Linstead and Noble, *J. Chem. Soc.*, **1937**, 933; (c) Ruggli and Peyer, *Helv. Chim. Acta*, **9**, 929 (1926); (d) Gilman, Hewlett, and Wright, *J. Am. Chem. Soc.*, **53**, 4192 (1931); (e) Schofield and Simpson, *J. Chem. Soc.*, **1945**, 512.

¹⁷ Krafft and Reuter, *Ber.*, **25**, 2243 (1892).

¹⁸ (a) Slummer, *Ber.*, **36**, 289 (1903); (b) Jacobs, Cramer, and Weiss, *J. Am. Chem. Soc.*, **62**, 1849 (1940); (c) Jacobs, Cramer, and Hanson, *Ibid.*, **64**, 223 (1942).

¹⁹ Lespieau and Bourguet, *Org. Syntheses, Coll. Vol. 1*, 209, 2nd ed., 1941; Lespieau, *Ann. chim. phys.*, [7] **11**, 232 (1897); *Bull. soc. chim. France*, [4] **29**, 528 (1921).

²⁰ Hessler, *Org. Syntheses, Coll. Vol. 1*, 438, 2nd ed., 1941.

²¹ von Hevesy, *Z. physik. Chem.*, **73**, 667 (1910).

²² Pickering, *J. Chem. Soc.*, **63**, 590 (1893).

ordinary reagent grade usually contains enough water to melt at about 200° . For many reactions it is simpler to use a mixture of 2 parts of potassium hydroxide and 1 part of sodium hydroxide, which melts below 200° .²³ The eutectic of these alkalis lies close to 50% by weight and melts at 187° ,²¹ but the presence of water lowers the melting temperature. Glass vessels are not attacked appreciably by solid potassium hydroxide, but molten alkali is very corrosive and glass flasks (especially Pyrex) can be used safely no more than three or four times. If a Wood's metal bath is used for heating, the run can be completed even if the flask is eaten through below the bath level, but an oil bath is very rapidly saponified and usually foams over when the flask breaks. It is said that the use of steel or copper flasks reduces the yield slightly,²⁰ but a 70% yield of phenylacetylene is reported using a copper vessel and a stream of dry air to remove the phenylacetylene vapors.²² Copper flasks have been used successfully in other reactions.¹²

A mineral-oil suspension of powdered potassium hydroxide has been used to give a high yield of alkynes (partially rearranged.)²⁴ The method has not been applied to the synthesis of arylacetylenes.

Sodium Amide

Meunier and Desparmet were the first to use sodium amide to produce a triple bond; they dropped ethylene dibromide onto the *powdered reagent* and obtained acetylene.²⁵ Later, they studied the dehydrohalogenation of higher homologs of ethylene dibromide. These results were submitted to the French Chemical Society in a sealed communication. After Bourguel²⁶ independently made the same discovery, Meunier and Desparmet published the details of their work.²⁷ Bourguel has supplied carefully tested directions for the synthesis by this procedure of a variety of 1-alkynes.^{25, 23, 28}

The following types of halogen compounds are suitable starting materials: RCHXCH_2X , RCH_2CHX_2 , RCX_2CH_3 , $\text{RCX}=\text{CH}_2$, and $\text{RCH}=\text{CHX}$. The halide is added dropwise to an excess of finely pulverized sodium amide *in an inert solvent* at 110 – 160° . Ammonia is given off vigorously at first, and the reaction is complete when this

²² (a) Rupe and Rinderknecht, *Ann.*, **442**, 61 (1925); (b) Hurd and Cohen, *J. Am. Chem. Soc.*, **53**, 1068 (1931).

²⁴ (a) Guest, *J. Am. Chem. Soc.*, **50**, 1744 (1928); (b) Bachman and Hill, *ibid.*, **56**, 2730 (1934); (c) Hall and Bachman, *Ind. Eng. Chem.*, **28**, 57 (1936).

²⁵ Meunier and Desparmet, *Bull. soc. chim. France*, [4] **1**, 342 (1907).

²⁶ Bourguel, *Compt. rend.*, **176**, 751 (1923).

²⁷ Meunier and Desparmet, *Bull. soc. chim. France*, [4] **35**, 481 (1924).

²⁸ Bourguel, *Ann. chim.*, [10] **3**, 191, 325 (1925).

²⁹ Lespieau and Bourguel, *Org. Syntheses, Coll. Vol. 1*, 191, 2nd ed., 1941.

evolution becomes very slow; the reaction requires about twenty hours at 110°, three to four hours at 130°, and only fifteen minutes after all the halide is added at 160°. A temperature of 150–165° is most satisfactory, and a purified petroleum oil, none of which boils below 250°, is the most readily available solvent. Different ligroin fractions, the lightest boiling at 150–180° and the heaviest at 125–140°/14 mm., have been used,²³ with no advantages recorded for any particular fraction. Xylene and toluene have been employed, but the long refluxing is a disadvantage especially with the latter. Usually the mixture is heated for two hours after all the halide is added to ensure completion of the reaction. The acetylene forms a solid complex with excess sodium amide, and volatile impurities such as olefins may be removed under reduced pressure or by distillation of part of the solvent when it is not too high boiling. The acetylene is then liberated with dilute hydrochloric acid or acetic acid.^{30,31} The yields are usually 60–85% as summarized in Table I. Bourguet did not use a mechanical stirrer, though efficient stirring was employed when the reaction was carried out in mineral-oil suspensions.

TABLE I
DEHYDROHALOGENATION WITH SODIUM AMIDE³²

| Acetylene | Starting Material | Yield % |
|------------------------|-------------------------------|---------|
| 1-Butyne ³³ | Bromobutene mixture | 60 |
| 1-Pentyne | $C_2H_5CH=CClCH_3$ | 62 |
| | $C_2H_7CCl_2CH_3$ | 45 |
| | $C_3H_7CBr=CH_2$ | 55 |
| | $C_2H_5CCl=CHCH_3$ | 30 |
| | $C_2H_5CCl_2C_2H_5$ } mixture | |
| 1-Hexyne | $C_4H_9CBr=CH_2$ | 60 |
| 1-Heptyne | $C_6H_{13}CHCl_2$ | 60 |
| | $C_2H_7CCl=CHC_2H_5$ | 15* |
| 1-Octyne | $C_5H_{11}CHBr_2CHBrCH_3$ | 25 |
| | $C_6H_{13}CBr=CHCH_3$ | 55 |
| | $C_4H_9CBr=CH_2$ | 75 |
| Phenylacetylene | $C_6H_5CBr=CH_2$ | 75 |
| | $C_6H_5CHBrCH_2Br$ | 40, 60 |
| 3-Phenyl-1-propyne | $C_6H_5CH_2CBr=CH_2$ | 75 |
| 3-Cyclohexyl-1-propyne | $C_6H_{11}CH_2CBr=CH_2$ | 87 |

* The yield of disubstituted acetylene, mainly 3-heptyne, was 40%.

³⁰ Levina and Ivanov, *J. Gen. Chem. U.S.S.R.*, **7**, 1866 (1937) [*C.A.*, **32**, 507 (1938)].

³¹ Levina and Kulikov, *J. Gen. Chem. U.S.S.R.*, **10**, 1189 (1940) [*C.A.*, **35**, 2881 (1941)].

³² Bourguet, *Bull. soc. chim. France*, [4] **41**, 1475 (1927).

The lower yield of 3-cyclohexylpropyne obtained with mineral oil as a medium²⁹ as compared with a petroleum fraction boiling at 180–220°²³ may be accounted for by the difficulty of removing the reaction product from the former medium. Table II gives the yields reported with mineral oil and certain other solvents.

TABLE II
DEHYDROHALOGENATION WITH SODIUM AMIDE

| Acetylene | Starting Material | Yield % | Reference |
|--|---|----------|-----------|
| 1-Butyne | 2,2-Dichlorobutane | 40 * | 33 |
| 3-Methyl-1-butyne | 3-Methyl-2-butanone | 6 † | 34 |
| | 1- and 2-Bromo-3-methylbutene | 25 † | 34 |
| | 1,2-Dibromo-3-methylbutane | 23–34 | 35, 36 |
| 1-Heptyne | 1-Chloroheptene | 60–70; ‡ | 4, 37 |
| | | 54 | |
| | Chloro compounds from heptaldehyde | 50–80 | 27 |
| 4,4-Dimethyl-1-pentyne | 2-Bromo-4,4-dimethyl-1-pentene | 37 | 38 |
| 3-Ethyl-3-methyl-1-pentyne | 2-Chloro-3-ethyl-3-methyl-1-pentene | 45 | 39 |
| 1-Nonyne | Chloro compounds from 2-nonanone | 50–80 | 27 |
| 1-Decyne | 2-Bromo-1-decene | 68 | 4, 29 |
| 1-Undecyne | Chloro compounds from 2-undecanone | 50–80 | 27 |
| 1-Hexadecyne | 1,2-Dibromohexadecane | 65 | 40 |
| Cyclopentylacetylene | Cyclopentyl methyl ketone | 9 ‡ | 41 |
| Cyclohexylacetylene | Cyclohexanol (5 steps) | 6 ‡ | 41 |
| 3-Cyclohexyl-1-propyne | 2-Bromo-3-cyclohexyl-1-propene | 66 | 29 |
| 4-Cyclohexyl-1-butyne | 4-Cyclohexyl-1,2-dibromobutane | 65 ¶ | 30 |
| 3-Cyclopentyl-1-propyne | 3-Cyclopentyl-2-bromo-1-propene | 65 | 41 |
| 3-(<i>cis</i> - β -Decalyl)-1-propyne | 3-(<i>cis</i> - β -Decalyl)-1,2-dibromopropane | 77 ¶ | 31 |
| 3-(<i>trans</i> - β -Decalyl)-1-propyne | 3-(<i>trans</i> - β -Decalyl)-1,2-dibromopropane | 86 ¶ | 31 |
| <i>p</i> -Tolylacetylene | α -Chloro- <i>p</i> -methylstyrene | 30 | 42 |
| 2,4-Dimethylphenyl acetylene | α -Chloro-2,4-dimethylstyrene | 75 | 43 |
| Mesitylacetylene | α -Chloro-2,4,6-trimethylstyrene | 71 | 43 |
| 4-Phenyl-1-butyne | 2-Bromo-4-phenyl-1-butene | 63 | 4, 29 |
| | 1,2-Dibromo-4-phenylbutane | 55 | 44, 44a |
| Tolan | α -Chlorostilbene | 34 | 45 |

* Allowing for 25% recovery of chlorobutene.

† The medium was not stated.

‡ Obtained 50% of the designated acetylene.

§ The medium was decalin.

¶ The medium was benzene.

REFERENCES TO TABLE II

- ¹² Stoll and Rouvé, *Helv. Chim. Acta*, **21**, 1542 (1938).
¹³ Grédy, *Bull. soc. chim. France*, [5] **2**, 1951 (1935).
¹⁴ Dedusenko, *Trudy Akad. Nauk S.S.S.R., Azerbaidzhan Filial*, 1940, No. 3, 87; *Khim. Referat. Zhur.*, **4**, No. 1, 43 (1941) [*C.A.*, **37**, 1697 (1943)].
¹⁵ Dedusenko, *Trudy Khim. Inst. Azerbaidzhan. Filiala Akad. Nauk*, **4**, No. 1, 15 (1940); *Khim. Referat. Zhur.*, **4**, No. 9, 53 (1941) [*C.A.* **38**, 1466 (1944)].
¹⁶ Guest, *J. Am. Chem. Soc.*, **47**, 860 (1925).
¹⁷ Osanno and Marvel, *J. Am. Chem. Soc.*, **52**, 5267 (1930).
¹⁸ Davis and Marvel, *J. Am. Chem. Soc.*, **53**, 3840 (1931).
¹⁹ Mulliken, Wakeman, and Gerry, *J. Am. Chem. Soc.*, **57**, 1605 (1935).
²⁰ Grédy, *Ann. chim.*, [11] **4**, 5 (1935).
²¹ Willemart, *Bull. soc. chim. France*, [4] **45**, 644 (1929).
²² Vaughn and Nieuwland, *J. Am. Chem. Soc.*, **56**, 1207 (1934).
²³ Levina and Panov, *J. Gen. Chem. U.S.S.R.*, **11**, 533 (1941) [*C.A.*, **35**, 6036 (1941)].
²⁴ Paillard and Wieland, *Helv. Chim. Acta*, **21**, 1356 (1938).

It has been suggested²⁵ that the solid complex obtained in dehydrohalogenations with sodium amide contains some product different from the simple sodium acetylide, for it cannot be carbonated or methylated in high yield and the ammonia liberated during its formation is less than required by the following equation.



However, 2-pentynoic acid was obtained in 46% yield by treating 1,2-dibromobutane with sodium amide in kerosene at 145°, diluting the reaction mixture with ether, and passing in carbon dioxide with cooling.²⁶ When the starting material was the chlorinated mixture obtained from 2-pentanone and phosphorus pentachloride, the yield of acid dropped to 2-3%.

Of special importance for the success of the synthesis is the *quality* of the sodium amide. On exposure to the air, the reagent acquires a protective coating of sodium hydroxide. The dehydrohalogenation is then brought about by the sodium hydroxide and is accompanied by rearrangement of the triple bond. Such coated sodium amide is incapable of converting a monosubstituted acetylene into its sodium derivative even at 100°, whereas with a pure reagent this reaction occurs rapidly in ether at 30° although the quantity of ammonia evolved indicates no more than 85-90% conversion. Bourguet²⁷ used sodium amide of good commercial grade in his experiments and took great care to grind and store it out of contact with moisture. Accurate directions have appeared for the preparation of sodium amide from

²⁵ Favorskii and Molhnach, *Bull. Far East. Branch Acad. Sci. U.S.S.R.*, **9**, 3 (1934) [*C.A.*, **29**, 3981 (1935)]; *J. Gen. Chem. U.S.S.R.*, **3**, 1663 (1935) [*C.A.*, **30**, 3404 (1936)].

molten sodium and anhydrous ammonia.⁴⁷ A rapid and convenient method for obtaining the reagent in liquid ammonia has been described⁴³ (p. 48). By adding this solution to mineral oil at room temperature and heating to drive off the ammonia, a reactive, finely divided suspension is obtained. The sodium oxide which is present appears to have no deleterious effect. A yellow color due to peroxide formation often develops in old sodium amide which has been exposed to air. This material is dangerously explosive and should be discarded at once.⁴⁷

Sodium amide in mineral oil has been reported⁴³ to be superior to ethanolic potassium hydroxide for the synthesis of mesityl- and 2,4-dimethylphenyl-acetylene, but it reacts too vigorously with halogen-substituted α -chlorostyrenes, and ethanolic alkali is better.^{43,49} For *p*-tolylacetylene the yields reported using potassium hydroxide^{50,51} are better than those with sodium amide, and the same is true for tolan^{5,45} and even for isopropylacetylene.²⁶

The sodium amide method has been recommended for the synthesis of 3-aryl-1-propynes;⁵² the yields were said to approach 75%. In view of the ease of rearrangement of these compounds to 1-aryl-1-propynes, (see p. 17), great care is necessary in the final hydrolysis of the reaction mixture.

Liquid ammonia offers a satisfactory medium for dehydrohalogenations,^{43a} although there is some indication that with dibromides olefin formation is an important side reaction. The method is not often used since ammonia is somewhat less convenient to handle than other solvents. Table III gives some of the results.

⁴⁷ Dennis and Browne, *Inorganic Syntheses*, I, 74 (1939); *J. Am. Chem. Soc.*, 26, 587, 597 (1904); Bergstrom and Fernelius, *Chem. Revs.*, 12, 52 (1933); Bergstrom, *Org. Syntheses*, 20, 86 (1940).

⁴³ (a) Vaughn, Vogt, and Nieuwland, *J. Am. Chem. Soc.*, 56, 2120 (1934); (b) Greenlee and Henne, *Inorganic Syntheses*, 2, 123 (1946).

^{43a} Dufraisse and Dequesnes, *Bull. soc. chim. France*, [4] 49, 1850 (1931).

⁵⁰ Smith and Hoehn, *J. Am. Chem. Soc.*, 63, 1175 (1941).

⁵¹ Robin, *Ann. chim.*, [10] 16, 421 (1931).

⁵² Bert, Dorier, and Lamy, *Compt. rend.*, 181, 555 (1925).

TABLE III *

ACTION OF SODIUM AMIDE ON HALOGEN COMPOUNDS IN LIQUID AMMONIA

| Halogen Compound | Product | Yield % | |
|-----------------------------------|-------------------------------|---------|-----------------|
| | | Overall | Accounted for † |
| 1-Iodo-1-hexyne | 1-Hexyno | 31 | 34 |
| 1,2-Dibromo-1-heptyne | 1-Heptyno | 55 | |
| 2-Bromo-1-octyne | 1-Octyno | 73 | 90 |
| 1,2-Dibromodecane | 1-Decyno | 54 | 78 |
| 2-Bromo-1-pentadecene | 1-Pentadecyno ³³ | 10 | |
| α -Chlorostyrene | Phenylacetylene | 57 | |
| β -Bromostyrene | Phenylacetylene | 75 | 83 |
| Styrene dibromide | Phenylacetylene ⁴⁴ | 52, 64 | |
| p-Methyl- α -chlorostyrene | p-Tolylacetylene | 49 | 64 |
| Stilbene dibromide | Stilbene | 86 | |

* This table is taken from Vaughn, Vogt, and Nieuwland, ref. 43a, except as indicated.

† The figures in this column are the yields after allowing for recovered starting material.

Other Alkaline Reagents

Other alkaline reagents are sometimes used for dehydrohalogenation, but these have usually been less satisfactory for preparing acetylenes although they often have advantages for preparing olefins. *Sodium hydroxide* is relatively insoluble in ethanol, but aqueous or dilute ethanolic solutions have been used.^{18, 4, 4, 55, 57} *Sodium ethoxide* was used in the original propyne synthesis;² it has been employed occasionally in the synthesis of substituted tolans (p. 40) or other arylacetylenes^{58, 59} but rarely for alkynes.^{60, 61, 62} An unusually interesting example of the

¹⁸ Ryden, Glavis, and Marvel, *J. Am. Chem. Soc.*, **55**, 1614 (1937).⁴ Campbell and O'Connor, *J. Am. Chem. Soc.*, **61**, 2997 (1939).⁴ Ruggli, Caspar, and Hegedüs, *Helv. Chim. Acta*, **20**, 250 (1937).⁵⁵ Bashford, Emeléus, and Briscoe, *J. Chem. Soc.*, 1938, 1358.⁵⁷ Hatch and Moore, *J. Am. Chem. Soc.*, **66**, 235 (1944); Hatch and Evans, Brit. pat. 582,764 [*C.A.*, **42**, 583 (1945)].⁵⁸ Adams and Theobald, *J. Am. Chem. Soc.*, **65**, 2208, 2383 (1943).⁵⁹ Adams and Ludington, *J. Am. Chem. Soc.*, **67**, 794 (1945).⁶⁰ Wislicenus and Hölz, *Ann.*, **250**, 230 (1889).⁶¹ Loevenich, Losen, and Dierichs, *Ber.*, **60**, 950 (1927).⁶² Bachman, *J. Am. Chem. Soc.*, **57**, 1088 (1935).

use of sodium ethoxide or hydroxide is the preparation of diacetylene from 1,4-dichloro-2-butyne.⁶²

Ketene acetals have been prepared⁶³ by dehydrohalogenation of haloacetals with *potassium tert-butoxide* in *tert*-butyl alcohol, which does not add to the reactive double bond, but no report of the use of this reagent for acetylene synthesis has appeared.⁶⁴ The use of *sodium anilide*,⁶⁵ *potassium benzyolate*,⁶⁶ and *sodium ethylmercaptide*^{67,68} can be mentioned, but only the first showed synthetic promise. The preparation of 1-nitro-1-butyne and 1-nitro-1-pentyne by treatment of the corresponding 1-bromo-1-nitroolefins with *methylamine* and *diethylamine* respectively has been reported.⁶⁷ Dibromosuccinic acid gives acetylenedicarboxylic acid when treated with aqueous solutions of *pyridine* or *quinoline*,⁶⁸ but, in general, amines are not basic enough to remove hydrogen halide from a haloethylene.⁶⁹ 1,2-Dibromo-3-cyclohexylpropane gives 3-cyclohexyl-1-propyne in 27% yield when treated with ethanolic potassium hydroxide but gives cyclohexylallene in unspecified yield when distilled with quinoline. Aqueous *potassium carbonate* has been used occasionally⁷⁰ and *alkaline-earth carbonates* or *hydroxides* have been employed to prepare acetylenedicarboxylic or halogenated phenylpropionic acids.⁷¹ Bromomaleic and bromofumaric acids yield propiolic acid merely by heating with water at 140°. ⁷² It has been shown that *sodium in liquid ammonia* removes halogen quantitatively

⁶² *Synthetic Fiber Developments in Germany*, Textile Research Institute, New York, 1946, p. 549.

⁶³ Beyersdorf and McIlwain, *J. Am. Chem. Soc.*, **58**, 529 (1936).

⁶⁴ (a) Potassium *tert*-butoxide was less satisfactory than distillation from powdered potassium hydroxide for the dehydrohalogenation of bromophenoxymethylene to phenoxycetylene, although a low yield was obtained. Unpublished work, Jacobs and Whitaker. (b) Addition of *tert*-butyl alcohol to a triple bond may be involved in the formation of β -*tert*-butoxyacetylenic acid by the action of potassium *tert*-butoxide on α -bromocrotonic acid. Owen, *J. Chem. Soc.*, 1945, 385.

⁶⁵ Bodroux, *Compt. rend.*, **203**, 1022 (1937).

⁶⁶ Rieckeghem, *Bull. soc. chim. Belg.*, **47**, 261 (1938).

⁶⁷ Loewenich, Koch, and Puckman, *Ber.*, **63**, 636 (1930).

⁶⁸ Dubrunf, *Bull. soc. chim. France*, [3], **31**, 914 (1904); *Compt. rend.*, **137**, 1063 (1903).

⁶⁹ Levine and Trakhtenberg, *J. Gen. Chem. U.S.S.R.*, **6**, 764 (1935); *Coll.*, **30**, 6395 (1935).

⁷⁰ (a) Orskoff and Tiffeneau, *Bull. soc. chim. France*, [4], **37**, 1410 (1925); (b) Carlier and Einhorn, *Ber.*, **23**, 2894 (1890), reported that treatment of β -(2-quinolyd)acrylic acid dichloride with aqueous alkaline carbonate gave 2-quinolylacetylene; (c) Alberus and Richman, *J. Am. Chem. Soc.*, **57**, 1294 (1935), were unable to duplicate the result reported in (b).

⁷¹ (a) Jackson and Hill, *Ber.*, **11**, 1571 (1878); *Hilf. Am. Chem. J.*, **3**, 95 (1881); (b) Walloch, *Ann.*, **203**, 53 (1880); (c) Lossen, *Ann.*, **272**, 127 (1893); (d) Lossen and Mendel, *Ann.*, **345**, 308 (1907).

reported occasionally; for example, 10-undecyne-1-al diethyl acetal^{7a} and 4-pentynoic acid.^{7b} The synthesis of disubstituted acetylenes, the purity of which was undetermined, has been reported many times, as illustrated by 4-methyl-2-pentyne^{7c} and 2-methyl-4-hexyne.^{7d} Ethanolic sodium hydroxide and sodium ethoxide effect the shift, but solid potassium hydroxide does not at the temperatures used. Allene or methylacetylene gives mainly ethyl isopropenyl ether, and dipropargyl is changed in low yield to dimethyldiacetylene. Favorskii believed that the rearrangement goes to completion since his products gave no precipitate with ammoniacal silver or cuprous solutions; however, later workers obtained indications, with the more sensitive ethanolic silver nitrate, of incomplete conversion.^{17,50} Higher 1-alkynes rearrange mainly to 2-alkynes.^{17,50,51} It is reported⁵² that samples of 2-octyne prepared by rearrangement of 1-octyne and by the methylation of sodium amylacetylide have identical physical properties and Raman spectra.

At 380°, 1-heptyne rearranges in the vapor state over soda lime to a disubstituted acetylene to a considerable extent, but the change is slight at 250°.^{24,71} Over pumice at 350° less rearrangement but much decomposition occurs.

The reverse change of a disubstituted acetylene or allene into a monosubstituted acetylene by heating in a sealed tube with sodium at 100° has been effected.⁵³ The product, the sodium alkynide, was an almost dry powder which could be carbonated to the acetylenic acid or decomposed with water to the alkyne. Higher temperatures than 100° are generally found necessary for this reaction^{17,53} and some olefin is produced by hydrogenation.^{52,53} Sodium amide brings about the same change.^{17,53} The conditions for the rearrangement are not greatly different from those employed with sodium, but sodium amide is preferable because the triple bond is not reduced. The reaction is usually carried out with a suspension of the reagent in an inert solvent, and temperatures as low as 110° have been used, although the best results are obtained at 150–160°.

^{7a} (a) English and Velick, *J. Am. Chem. Soc.*, **67**, 1413 (1945); (b) Schjlenberg, *Ber.*, **71**, 569 (1938); (c) Ipatieff, *J. Russ. Phys. Chem. Soc.*, **27**, 357 (1895); *J. prakt. Chem.*, [2] **53**, 145 (1895); (d) Petrov, Verbitsova and Kokeleva, *J. Gen. Chem. U.S.S.R.*, **11**, 1095 (1941) [*C.A.*, **37**, 3732 (1943)].

⁵⁰ (a) Béal, *Bull. soc. chim. France*, [2] **49**, 551 (1885); (b) Wislicenus and Schmidt, *Ann.*, **313**, 210 (1900).

⁵¹ Kraff, *Ber.*, **29**, 2232 (1895).

⁵² Favorskii, *J. Russ. Phys. Chem. Soc.*, **19**, 553 (1887) (*Chem. Zentr.*, 1888, 242); *J. prakt. Chem.*, [2] **37**, 417 (1885); *J. Russ. Phys. Chem. Soc.*, **50**, 43 (1918) [*C.A.*, **18**, 2495 (1924)].

⁵³ Béal, *Bull. soc. chim. France*, [2] **50**, 623 (1885).

When sodium amide is used for dehydrohalogenation a complete rearrangement of disubstituted to monosubstituted acetylenes does not always occur, but Bourguet²³ effected a clean separation of these products by working in a ligroin fraction which boiled higher than the acetylenes but low enough for partial removal by distillation. When the dehydrohalogenation was over, as indicated by cessation of ammonia evolution, the disubstituted acetylenes were removed with some of the solvent under reduced pressure before the sodium derivative of the monosubstituted acetylene was decomposed. Table IV indicates the yields

TABLE IV
REARRANGEMENT OF ACETYLENES BY SODIUM AMIDE *

| Starting Material | Amt. g. | NaNH ₂ g. | Temp. °C. | Time hr. | Solvent | Recovered Starting Material | Mono-substituted Acetylene g. | Yield % | |
|------------------------|---------|----------------------|-----------|----------|----------------------------------|-----------------------------|-------------------------------|---|---------------------------|
| | | | | | | | | Subtracting Recovered Starting Material | No Allowance for Recovery |
| 2-Octyne | 12 | 8 | 150 | 1½ | Pseudocumene | Very little | 9.5 | | 80 |
| 2-Nonyne | 18 | | 160 | 2 | Petroleum (b.p. 180-230°) | 2.5 g. (14%) | 13.0 | 84 | 73 |
| 3-Heptyne | 10 | | 170 | 4 | Pseudocumene | 4.0 g. (40%) | 3 to 4 | 50 to 55 | 30 to 40 |
| 3-Octyne | 22 | | 170 | 9 | Petroleum | 9.5 g. (43%) | 10.0 | 80 | 45 |
| 1-Phenyl-1-propyne | 8 | | 110 | 2 | Toluene | | 6.0† | | 67 |
| 1-Cyclohexyl-2-butyne | 215 | 80 | 160 | 2½ | Petroleum (b.p. 220-250°) | 8.0 g. (4%) | 185.0 | 80 | 77 |
| 5-Cyclohexyl-2-pentyne | 107 | 39 | 160 | 2½ | Petroleum (b.p. 125-140°/15 mm.) | 15.0 g. (14%) | 81.0 | 83 | 76 |
| 6-Cyclohexyl-2-hexyne | 48 | | 160 | 2½ | Petroleum (b.p. 125-140°/15 mm.) | 9.0 g. (18%) | 34.0 | 87 | 71 |

* Heating was discontinued when the evolution of ammonia became very slow. This usually occurred after 75% to 80% of the theoretical amount had been evolved. A slight excess of sodium amide was used (1.2 moles per mole of disubstituted acetylene) suspended in 300-400 ml. of solvent.

† No careful attempt was made to separate mono- from di-substituted acetylenes, although all the product was believed to be 1-alkyne.

‡ The first three-hour heating left 40 g. of disubstituted product, which, after reheating with fresh sodium amide, left only 8 g. of unchanged starting material.

and conditions in these experiments. It was observed that the rates of rearrangement vary with different compounds, but 3-alkynes always change more slowly than 2-alkynes. By essentially the same procedure, the allenes 1,2-pentadiene, 1,2-heptadiene, and 5-methyl-1,2-hexadiene give excellent yields of 1-pentyne, 1-heptyne, and 5-methyl-1-hexyne.

respectively.⁸⁴ The reaction is practically complete within two hours at bath temperatures of 140°.

A heptyne mixture containing 80% disubstituted compounds may be rearranged^{24a} by heating for twelve hours at 160° in a mineral-oil suspension of sodium amide with vigorous stirring, and an acetylene fraction (in unspecified yield) containing 64% of 1-heptyne is isolated.⁸⁵ This result is not inconsistent with those of Bourguet.²³ 6-Dodecyne and 5-decyne have been similarly rearranged at 210°.⁸⁶ This is the only recorded example of the shifting of a triple bond by five positions. In general, temperatures above 170° are undesirable because the sodium amide particles tend to clump together and the rearrangement is much slower. Sodium amide melts at 210°.⁴⁷

Because of this rearrangement it is possible to use compounds with halogens three and four carbons from the end of the chain for the synthesis of monosubstituted acetylenes, but the yields are generally less satisfactory as Table I shows.

Successive methylation of a sodium acetylide by dimethyl sulfate and rearrangement of the methylalkylacetylene to a new monosubstituted acetylene is a satisfactory method of synthesizing relatively inaccessible higher acetylenes. Using this method Bourguet was able to prepare 200 g. of 6-cyclohexyl-1-hexyne from 500 g. of 3-cyclohexyl-1-propyne by three repetitions of the cycle.

Since 3-nonyne is not rearranged by standing for sixteen hours at -34° in a liquid ammonia solution containing sodium amide,^{43a} it was suggested that easily rearranged disubstituted acetylenes might be synthesized by dehydrohalogenations in this medium, but no experimental work has been reported. Because 3-alkynes are less readily rearranged than 2-alkynes it would be interesting to observe the behavior of 2-nonyne or a similar compound in such a solution.

The rearrangement of the triple bond has been compared with a corresponding shift of the double bond.^{24c} Olefins have been studied mainly in the vapor phase or in acids,⁵⁷ and there is no evidence that 1-alkenes tend to rearrange to 2-alkenes in the presence of alkaline reagents under conditions comparable to those of the acetylene isomerization. However, at 420°, 1-butene is converted to 2-butene to the

⁸⁴ Bouis, *Ann. chim.*, [10] 9, 402 (1928).

⁸⁵ Analysis by the method of Hill and Tyson, ref. 74.

⁸⁶ Vaughn, *J. Am. Chem. Soc.*, 55, 3453 (1933).

⁸⁷ The isomerization of olefins and acetylenes has been reviewed by Egloff, Hulla, and Komarewsky, *Isomerization of Pure Hydrocarbons*, American Chemical Society Monograph, Reinhold Publishing Corp., New York, 1942, especially Chapters 2 and 3. A brief account is given by Egloff, *The Reactions of Aliphatic Hydrocarbons*, Chapter I of *Organic Chemistry*, Gilman, 2nd ed., John Wiley & Sons, New York, 1943.

extent of 92% by passage over lime.⁸⁸ It is well known that alkaline reagents cause a rearrangement of allyl benzenes to propenylbenzenes.⁸⁹ Similarly benzylacetylene cannot be prepared using solid or ethanolic potassium hydroxide,^{90,91} and even the reaction of benzyl chloride and sodium acetylide yields methylphenylacetylene.⁹⁰ The rates of interconversion by ethanolic sodium ethoxide and the positions of equilibrium in a series of substituted 1,3-diphenylpropenes have been determined, and the mechanism of the reaction has been discussed.⁹² In the acetylene series, 1-*p*-bromophenyl-3-phenyl-1- or 2-propynes ($\text{BrC}_6\text{H}_4\text{C}\equiv\text{CCH}_2\text{C}_6\text{H}_5$, $\text{BrC}_6\text{H}_4\text{CH}_2\text{C}\equiv\text{CC}_6\text{H}_5$) were found to be isolable compounds which were not isomerized by hot 15% potassium hydroxide solution or by the Grignard reagent.⁹³

The interconversion of α,β - and β,γ -olefinic acids has been studied,^{79a,94} but the corresponding rearrangements of acetylenic acids have not been reported.

The conversion of 1,4-dichloro-2-butyne to diacetylene⁹⁵ has already been mentioned (p. 12); this is presumably the result of 1,4-dehydrohalogenation rather than rearrangement.



Removal of Adjacent Halogen Atoms. When the starting material for acetylene synthesis is a 1,2-dihalogen compound the alkaline reagent sometimes removes the halogen atoms to form an olefin. This reaction is relatively common with the dihalides of stilbenes^{18a,70a,96} or β -aryl-acrylic acids^{70a,96} and has been observed more often with tertiary amines than with ethanolic potassium hydroxide, although α -iodo- β -chlorobutyric acid gives crotonic acid with ethanolic potassium hydroxide and α -iodocrotonic acid with pyridine.⁹⁷ β -(2-Quinoly)- and β -(4-

⁸⁸ I.G. Farbenind. A.-G., U. S. pat. 1,914,674 [C.A., 27, 4252 (1933)]; Ger. pat. 583,790 [C.A., 28, 1058 (1934)].

⁸⁹ Tiffeneau, *Compt. rend.*, 139, 481 (1904); Agajewa, *J. Russ. Phys. Chem. Soc.*, 37, 662 (1905) (*Chem. Zentr.*, 1905, II, 1017); Klages, *Ber.*, 39, 2587 (1906); and many others.

⁹⁰ Lespieau, *Bull. soc. chim. France*, [4] 29, 523 (1921).

⁹¹ Zeberg, *J. Gen. Chem. U.S.S.R.*, 5, 1016 (1935) [C.A., 30, 1023 (1936)].

⁹² Ingold and Piggott, *J. Chem. Soc.*, 121, 2381 (1922); Ingold and Shoppee, *ibid.*, 1929, 447; Shoppee, *ibid.*, 1930, 968; 1931, 1225. A review of this work and of a number of related investigations can be found in Baker, *Tautomerism*, George Routledge and Sons, Ltd., London, 1934; D. Van Nostrand Co., New York, 1934, p. 80.

⁹³ Johnson, Jacoby, and Schwartz, *J. Am. Chem. Soc.*, 56, 1885 (1933).

⁹⁴ Linstead, *J. Chem. Soc.*, 1930, 1603; Linstead and Noble, *ibid.*, 1934, 610, 614.

⁹⁵ (a) Zincke and Fries, *Ann.*, 325, 44 (1902); (b) Zincke and Wagner, *Ann.*, 335, 236 (1905); (c) Pfeiffer, *Ber.*, 45, 1810 (1912); (d) Pfeiffer and Krauer, *Ber.*, 46, 3655 (1913); (e) Reinhardt, *Ber.*, 46, 3598 (1913); (f) Harrison, *J. Chem. Soc.*, 1926, 1232.

⁹⁶ (a) Pfeiffer and Langenberg, *Ber.*, 43, 3039 (1910); (b) Perkin and Bellenot, *J. Chem. Soc.*, 49, 440 (1886).

⁹⁷ Ingold and Smith, *J. Chem. Soc.*, 1931, 2742.

pyridyl)-acrylic acids are obtained from their dibromides not only by the action of common bases but even by boiling with water or ethanol.^{72c} Cyclic compounds such as 1,2-dibromocyclohexane which cannot yield an acetylene lose halogen to give cyclic olefins as one of several reactions with quinoline.⁷³

The removal of adjacent halogens to form olefins is an important side reaction when dibromides are treated with sodium amide.⁷³ In Bourguel's technique the olefin is readily separated from the 1-alkyne, but the yields of the acetylene are often low and it is preferable to remove the first molecule of hydrogen bromide with ethanolic potassium hydroxide. Bromoolefins are not converted to olefins by sodium amide. Polymerization always accompanies the dehalogenation; 1,2-dibromopropane gives very little methylacetylene, some propylene, and mainly polymer even though sodium amide free from sodium is used.

Addition of Alcohols. Acetylenes in which the triple bond is activated by conjugation with such groups as phenyl or carboxyl add primary alcohols readily in the presence of sodium alkoxides.⁷² Addition is also observed with propargyl acetal¹²⁰ and ethers of acetylenic glycols.¹²¹ With phenylacetylene this reaction gives alkyl styryl ethers in high yield,^{72c} and the direction of addition is the reverse of that observed with reagents in the presence of acid. Alcohols add 1,4 to vinylacetylene in the presence of sodium alkoxides, and the products rearrange to 1-alkoxy-2-butyne.¹²² Secondary alcohols add slowly, and tertiary alcohols even more slowly. Rearrangement is the principal reaction observed when 1-alkynes are treated with ethanolic alkali,^{72,72c} although Moureu isolated from 1-heptyne a little high-boiling material which may have been formed by addition of ethanol. Allene or methylacetylene gives mainly ethyl isopropenyl ether.^{73b}

Small amounts of vinyl ethers have been reported occasionally in the synthesis of arylacetylenes by the reaction of ethanolic potassium hydroxide, and this reagent has been used instead of sodium ethoxide to promote the addition of ethanol.^{72,72c} It appears that the presence of some water decreases the ease of addition and that vinyl ether formation is not ordinarily an important side reaction during dehydrohalogenation to produce arylacetylenes, although it might be expected to interfere with the use of sodium ethoxide (p. 11).

⁷² Harries and Splawa-Neyman, *Ber.*, **42**, 693 (1909); Harries, *Ber.*, **45**, 809 (1912); Willstätter and Hatt, *Ber.*, **45**, 1464 (1912).

^{72c} (a) Nef, *Ann.*, **308**, 264 (1899); (b) Moureu, *Compt. rend.*, **137**, 259 (1903); (c) Moureu, *Bull. soc. chim. France*, [3] **31**, 493, 526 (1904); (d) Moureu and Lazennec, *Compt. rend.*, **42**, 335 (1906); *Bull. soc. chim. France*, [3] **35**, 526, 531 (1906).

¹²⁰ Claisen, *Ber.*, **36**, 3664 (1903).

¹²¹ Gauthier, *Ann. chim.*, [8] **16**, 289 (1909).

¹²² Jacobson, Dykstra, and Carothers, *J. Am. Chem. Soc.*, **56**, 1169 (1934).

Limitations in the Synthesis of Acetylenic Acids. Although substituted cinnamic acid dibromides or their esters are readily converted to phenylpropionic acids,¹⁰³ the reaction is usually accompanied by some decarboxylation. To minimize this side reaction the temperature is kept as low as possible, especially during acidification of the alkaline reaction mixture. The decarboxylation occurs readily and has been used for the synthesis of a number of substituted phenylacetylenes.^{14, 104} α -Alkylcinnamic acid dibromides yield 1-phenyl-1-alkynes directly and in good yield when treated with ethanolic potassium hydroxide.¹⁰⁵

Aliphatic acids with a triple bond adjacent to the carboxyl group cannot be prepared from the dibromides of the corresponding olefinic acids or from the α -haloolefinic acids. The action of alcoholic alkali on α -bromocrotonic or α,β -dibromobutyric acid gives α - and β -alkoxycrotonic acids in proportions depending upon the alcohol.^{41a, 106} The attempted synthesis of 2-pentynoic acid from 2-pentenoic acid dibromide failed,^{79a} and propionic acid has not been obtained from α,β -dihalo-propionic or α -haloacrylic acid although α -ethoxyacrylic acid, pyruvic acid, glyceric acid, and polymers have been reported.¹⁰⁷ The conversion of α -bromoacrylic acid to acetylene and carbon dioxide by dehydrohalogenation and decarboxylation has been noted.^{107b, 108}

Certain β -halo- α,β -unsaturated acids will yield acetylenic acids, for tetrolic acid is usually prepared from ethyl acetoacetate by the action of phosphorus pentachloride followed by potassium hydroxide;¹⁰⁹ but the yield is often low, and such by-products as acetone, ethoxycrotonic acid, and polymers are produced. The literature contains conflicting reports on the conversion of 3-bromo-2-pentenoic acid to 2-pentynoic acid.^{40, 79b} Most α,β -acetylenic carboxylic acids are now prepared by carbonation of metallic derivatives of 1-alkynes so that decarboxylation of these acids has no synthetic value. However, the decarboxylation has been reported to take place with excellent yields.¹¹⁰

¹⁰³ For phenylpropionic acid see Abbott, *Org. Syntheses*, **12**, 60 (1932); *Coll. Vol.* **2**, 515 (1943); Reimer, *J. Am. Chem. Soc.*, **64**, 2510 (1942).

¹⁰⁴ (a) Otto, *J. Am. Chem. Soc.*, **56**, 1393 (1934), (b) Fulton and Robinson, *J. Chem. Soc.*, **1933**, 1463; (c) Weltsien, Michael, and Hless, *Ann.*, **433**, 247 (1923); (d) Wollring, *Ber.*, **47**, 111 (1914); (e) Gattermann, *Ann.*, **247**, 347 (1906), (f) Straus, *Ann.*, **242**, 190 (1905); (g) Reyckler, *Bull. soc. chim. France*, [3] **17**, 513 (1897); (h) Müller, *Ann.*, **212**, 122 (1882); *Ber.*, **20**, 1212 (1887); (i) Baeyer, *Ber.*, **13**, 2254 (1880); (j) Glaser, *Ann.*, **154**, 137 (1870).

¹⁰⁵ Bogert and Davidson, *J. Am. Chem. Soc.*, **54**, 334 (1932).

¹⁰⁶ Pfister, Robinson, and Tishler, *J. Am. Chem. Soc.*, **67**, 2269 (1945).

¹⁰⁷ (a) Otto, *Ber.*, **23**, 1108 (1890), Otto and Beckurts, *Ber.*, **18**, 239 (1885); (b) Lossen and Kowski, *Ann.*, **342**, 124 (1905); (c) Wagner and Tollens, *Ann.*, **171**, 340 (1874).

¹⁰⁸ Mauthner and Suida, *Monatsh.*, **2**, 98 (1881).

¹⁰⁹ See table, p. 23.

¹¹⁰ Moureu and André, *Ann. chim.*, [9] **1**, 116 (note) (1914).

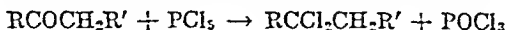
Acetylenedicarboxylic acid⁹ resembles phenylpropionic acid in that it is prepared from α,β -dibromosuccinic acid without difficulty and its acid potassium salt is readily decarboxylated to propionic acid.¹¹¹

Other Side Reactions. Polymerization is encountered in the synthesis of a number of acetylenic compounds, and autoxidation may occur,^{112,113} although usually it is not important. The formation of polymeric material under the influence of ethanolic potassium hydroxide, sodium ethoxide, and similar reagents may perhaps be the result of polymerization of vinyl ethers formed by addition of alcohol to the triple bond.

Preparation of the Halogen Compounds for Dehydrohalogenation to Acetylenes

Four general methods have been employed for synthesis of halogen compounds useful for preparing acetylenes: (1) olefins to olefin dibromides, (2) cinnamic acids to ω -bromostyrenes, (3) ketones with phosphorus pentachloride to dihalides, (4) 2-bromoallyl bromide or 3-chloroallyl chloride with Grignard reagents to halogenated olefins. The first method requires no comment. The second has been reviewed in a previous chapter in *Organic Reactions*.¹¹⁴ The third and fourth will be discussed below.

Phosphorus Pentachloride and Carbonyl Compounds. The reaction of phosphorus pentachloride with carbonyl compounds¹¹⁵ has been widely used to prepare chlorides for acetylene synthesis. The products of the reaction include monochloroethylenes as well as the expected dichlorides; hydrogen chloride is always produced. Favorskii¹¹⁶ has re-



viewed the work prior to 1913 and has carefully studied the reaction with aliphatic ketones. Maximum yields of chlorides suitable for acetylene synthesis are obtained by adding the ketone dropwise to a slight excess

¹¹¹ (a) Bandrowski, *Ber.*, **13**, 2340 (1880); (b) Baeyer, *Ber.*, **18**, 674, 2269 (1885); (c) Perkin and Simonsen, *J. Chem. Soc.*, **91**, 816 (1907); (d) Ingold, *J. Chem. Soc.*, **127**, 1199 (1925); (e) for an alternative preparation see Straus and Voss, *Ber.*, **59**, 1681 (1926); Straus, Heyn, and Schwemer, *Ber.*, **63**, 1086 (1930).

¹¹² Young, Vogt, and Nieuwland, (a) *J. Am. Chem. Soc.*, **56**, 1822 (1934); (b) *ibid.*, **58**, 55 (1936); (c) *J. Chem. Soc.*, 1935, 115.

¹¹³ Campbell and Eby, *J. Am. Chem. Soc.*, **63**, 216 (1941).

¹¹⁴ The Perkin Reaction, Johnson, *Org. Reactions*, **1**, 210-265 (1942).

¹¹⁵ Friedel, *Compt. rend.*, **67**, 1192 (1868); *Ann. chim.*, [4] **16**, 310 (1869).

¹¹⁶ Favorskii, *J. prakt. Chem.*, [2] **88**, 641 (1913); *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912) [*C.A.* **7**, 934 (1913)].

of phosphorus pentachloride in an all-glass apparatus at 0° so that the evolution of hydrogen chloride is not vigorous. The reaction occurs only at higher temperatures with diisopropyl ketone or pentamethylacetone, and under these conditions α -chloroketones are formed as the result of a chlorination reaction. Pinacolone is converted to a mixture of chloroolefin and dichloride which is readily transformed into *tert*-butylacetylene.^{4,116} The yield of chloro compounds has been reported as essentially quantitative, and the yield of *tert*-butylacetylene as 65%. Other workers have not always obtained such good results,^{4,117} although over 90% yields of chloro compounds have been obtained.¹¹⁷ By use of finely powdered phosphorus pentachloride, maintenance of the temperature at $0-5^\circ$, and stirring, the yield of mono- and di-chlorides is 91%, from which an 80% yield of the acetylene is obtained.¹¹⁷ The reaction of pinacolone with phosphorus pentachloride has been extensively studied.^{117,4} The only product isolated from ethyl *tert*-butyl ketone and phosphorus pentachloride at 70° is 2-chloro-4,4-dimethyl-3-pentanone, $(\text{CH}_3)_3\text{CCOCHClCH}_3$.¹¹⁸

Phosphorus pentabromide produces from all types of ketones mainly α -bromoketones and cannot be used to prepare bromides suitable for acetylene synthesis.¹¹⁴ This may be the result of the action of halogen formed by dissociation of the phosphorus pentabromide. However, the ketones are more readily brominated by phosphorus pentabromide than by bromine, so that, if the free halogen is the reagent, a phosphorus halide must be a catalyst for the reaction.

Even at 0° the products of the reaction of phosphorus pentachloride with aliphatic ketones include small amounts of dichloro compounds of the type RCHClCHClR' and of acetylenes as well as the expected dichloro compounds $\text{RCH}_2\text{CCl}_2\text{R'}$ and monochloroolefins.¹¹⁹ The chloroethylenes from methyl ketones are largely 2-chloro-2-alkenes, $\text{RCH}=\text{CClCH}_3$.¹¹⁹ However, butanone was said to give a mixture of chlorobutenes containing an appreciable amount of 2-chloro-1-butene.¹²⁰

The action of phosphorus pentachloride on arylacetones, $\text{ArCH}_2\text{COCH}_3$, gives a mixture of chloroolefins, $\text{ArCH}=\text{CClCH}_3$ and $\text{ArCH}_2\text{CCl}=\text{CH}_2$. If either of these pure chloroolefins is allowed to stand, it slowly changes to an equilibrium mixture of the two.¹²¹ An aromatic aliphatic ketone

¹¹⁷ (a) de Graef, *Bull. soc. chim. Belg.*, **34**, 427 (1925); (b) Bartlett and Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942); (c) Delacroix, *Bull. soc. chim. France*, [3] **35**, 343 (1906); *Acad. roy. Belg., Classe sci., Mém.*, [2] **1**, 1 (1904-1906); (d) Risseghem, *Bull. soc. chim. Belg.*, **31**, 62 (1922).

¹¹⁸ Vassiliev, *Bull. soc. chim. France*, [4] **43**, 563 (1928).

¹¹⁹ Bourguet, *Bull. soc. chim. France*, [1] **35**, 1629 (1924).

¹²⁰ Charpentier, *Bull. soc. chim. France*, [5] **1**, 1407 (1934).

¹²¹ Zakl and Iskander, *J. Chem. Soc.*, 1943, 68.

such as acetophenone yields mainly chloroethylene and polymer, but a little 1,1-dichloroethylbenzene can be isolated. Phosphorus trichloride dibromide¹²² gives a mixture of products including phenacyl bromide and phenacyl dibromide. A 54% yield of chlorostyrene is obtained¹²³ using petroleum ether as a solvent and mixing the phosphorus pentachloride with coarsely broken glass. The autoxidizability of the product is reported. Phosphorus oxychloride or a mixture of this with phosphorus trichloride has been used as a solvent in the reaction of acetobromomesitylene or acetoisodurene with phosphorus pentachloride.^{53,59} α -Chloroketones and phosphoric esters are reported as by-products.

In general the reaction of aromatic methyl ketones with phosphorus pentachloride is a satisfactory method of preparing intermediates for acetylene syntheses, since the starting materials are readily available by the Friedel and Crafts or other reactions, and there is no possibility of rearrangement of the triple bond in the final step. The reaction is usually carried out at about 70°. Aliphatic acetylenes are obtainable in this way in low yield only, except for a few compounds like *tert*-butylacetylene. Cyclohexylacetylene is readily obtainable by this method, but the yield of cyclopentylacetylene appears to be low. Table V gives some of the more recent results obtained. The preparation of *p*-tolylacetylene by this method is described in the section on laboratory procedures (p. 50).

Reaction of Grignard Reagents with Halogen-Substituted Allyl Halides. The reaction of 2,3-dibromopropene with Grignard reagents was first used by Lespieau⁵⁹ to prepare halogen compounds for acetylene syntheses. The reaction has been carefully studied,⁷³ and detailed directions for the synthesis of 3-cyclohexyl-2-bromopropene have been

¹²² Taylor, *J. Chem. Soc.*, 1937, 304.

¹²³ Dufraisse and Viel, *Bull. soc. chim. France*, [4] 37, 574 (1925).

TABLE V

YIELDS IN THE REACTION OF PHOSPHORUS PENTACHLORIDE WITH CARBONYL COMPOUNDS AND CONVERSION OF THE PRODUCTS TO ACETYLENES

| Acetylene | Yield of Chloro Compound % | Yield of Acetylene from Chloro Compound % | Overall Yield % | Reference |
|--|-------------------------------------|---|-----------------|-----------|
| Phenylacetylene | Quantitative yield of crude product | 37-43 | 37-43 | 99a |
| p-Tolylacetylene | 68 | 48 | 33 | 50 |
| | 75 | 57 | 43 | 51 |
| 2,4-Dimethylphenylacetylene | 82 | 75 * | 61 | 43 |
| Mesitylacetylene | 78 | 71 * | 55 | 43, 58 |
| 2,3,4,6-Tetramethylphenyl-acetylene | 73 † | 65 | 47 | 53 |
| p-Chlorophenylacetylene | 60 | 36 | 22 | 43 |
| p-Bromophenylacetylene | 70 | 53 | 37 | 40 |
| 3-Bromo-2,4,6-trimethylphenyl-acetylene | 63 | 57 | 36 | 58 |
| β-Naphthylacetylene | | | 35 | 51 |
| 2,4-Dimethyl-3-chloro-6-methoxyphenylacetylene | 60 | 60 | 36 | 59 |
| 3-Ethynyl-2-methylnaphthalene | | | 45 | 124 |
| Telan | 80 | 34 | 27 | 45 |
| Phenyl-β-naphthylacetylene | 75-93 † | 58 | 44-54 | 15 |
| β-Pyridylacetylene | 50 | 42 | 21 | 70c |
| Cyclopentylacetylene | | | 9 * | 41 |
| Cyclohexylacetylene | 70-80 | 46 | 32-37 | 125 |
| tert-Butylacetylene | 45-100 | 50-60 | 27-73 | 117 |
| 3-Ethyl-3-methyl-1-pentyne | 65 | 45 * | 20 | 30 |
| 1-Heptyne | 70 | 60 *† | 24 | 28, 74 |
| 4-Methyl-2-pentyne | | | 26 | 79c |
| 5-Methyl-2-hexyne | 61 | | | 79d |
| 2,6-Dimethyl-3-heptyne | 52 | 38 | 20 | 79d |
| Tetrollic acid | 52 | 16 | 15.5 § | 126 |
| 1-(p-Methoxyphenyl)-1-propyne | 24 | 75 | 18 | 127 |

* The sodium amide method was used for dehydrohalogenation.

† Crude product.

‡ Hull and Tyson, ref. 74, prepared 1,1-dichloroheptane in 70% yield but used it for vapor-phase dehydrohalogenation. Bourguet, ref. 28, obtained 60% yields of the acetylene using a rather pure chloro compound, and an overall yield of 24% in runs in which the chloro product was not purified carefully.

§ The overall yield was obtained in a larger run.

|| 2-Chloro-1-(p-anisyl)-1-propene from p-anisylacetone. p-Methoxypropionophenone was converted to 1-chloro-1-(p-anisyl)-1-propene in 44% yield, but this chloride was not dehydrohalogenated.

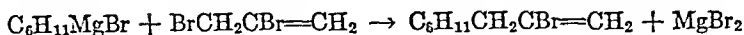
¹²⁴ Karrer, Epprecht, and König, *Helv. Chim. Acta*, **23**, 272 (1940).

¹²⁵ Sweet and Marvel, *J. Am. Chem. Soc.*, **54**, 1184 (1932).

¹²⁶ Feist, *Ann.*, **345**, 100 (1906).

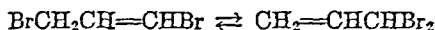
¹²⁷ Hobday and Short, *J. Chem. Soc.*, **1943**, 609.

described.^{123, 123} If the Grignard solution is added to the dibromopropene,

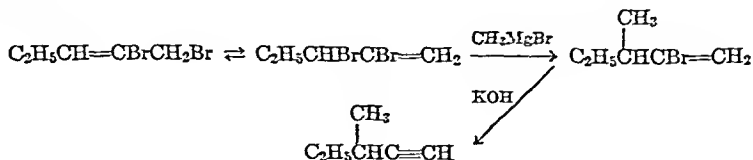


yields of 45–65% are usually obtained, but addition of the bromo compound to the organometallic derivative leads to the formation of complex substances and greatly reduces the yield of the desired product. Allene is one of the principal by-products. The presence also of a saturated bromo compound is attributed to the addition of the Grignard reagent to the double bond of $\text{RCH}_2\text{CBr}=\text{CH}_2$,⁹⁹ though some doubt about the saturated character of the by-product has recently been raised.¹²⁹

Syntheses with 1,3-dihalopropenes are complicated by the possibility of an allylic rearrangement which may lead to a mixture of products. The reaction of such allyl compounds with aliphatic Grignard reagents



is very complicated,¹³⁰ but nearly quantitative yields of 3-aryl-1-chloro-1-propenes have been reported^{32, 131} from arylmagnesium halides. α -Naphthylmagnesium bromide and 1,3-dibromopropene in toluene at 100°^{121c} give a 50% yield of product. The addition of 1,3- and 2,3-dibromo- and 1,3-dichloro-propenes to aryl Grignard reagents at low temperatures in ether results in lower yields than those reported above.¹³² The abnormal reaction of 1,2,3-tribromopropene with phenylmagnesium bromide will be discussed (p. 44). When the five-carbon homolog of bromoallyl bromide (mainly $\text{C}_2\text{H}_5\text{CH}=\text{CBrCH}_2\text{Br}$) is first converted to 3-bromo-3-hexene and then to 3-hexyne some 1-alkyne, presumably 3-methyl-1-pentyne, is obtained owing to an allylic rearrangement.¹³³



¹²³ Lespieau and Bourguet, *Org. Syntheses, Coll. Vol. 1*, 186, 2nd ed., 1941.

¹²⁹ Private communication, Young and Linden, University of California, Los Angeles.

¹³⁰ Kirmann, *Bull. soc. chim. France*, [4] 47, 834 (1930); Kirmann and Gard, *Compt. rend.*, 190, 876 (1930); Kirmann, Pacaud, and Dosque, *Bull. soc. chim. France*, [5] 1, 860 (1934); Kirmann and Renn, *Compt. rend.*, 202, 1934 (1936).

¹³¹ (a) Bert, *Bull. soc. chim. France*, [4] 37, 879 (1925); (b) *Compt. rend.*, 180, 1504 (1925); (c) Bert and Dorier, *Bull. soc. chim. France*, [4] 37, 1600 (1925); (d) *ibid.*, [4] 39, 1610 (1926).

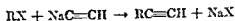
¹³² Braun and Kuhn, *Ber.*, 58, 2165 (1925).

¹³³ Lespieau and Wiemann, *Bull. soc. chim. France*, [4] 45, 627 (1929).

The halogen-substituted allyl halides such as 1,3-dichloropropene are readily prepared ^{13,124} by well-known methods.

1-ALKYNES FROM METALLIC DERIVATIVES OF ACETYLENE

The alkylation of sodium acetylide in liquid ammonia by alkyl halides was first reported by Lebeau and Picon.^{133,134} In this work alkyl iodides



were employed, but other alkyl halides have been used and the bromides usually give the best yields. Alkyl sulfates ^{137,138} and esters of *p*-toluenesulfonic acid ¹³⁹ have also been tried; dimethyl and diethyl sulfates are recommended for the synthesis of propyne and 1-butyne.^{140,141} The reaction is limited to the introduction of primary alkyl groups, $RC\equiv CH$, which are not branched on the second carbon. In the hands of an experienced operator yields of 70-90% are usually obtained. The method has been extensively investigated and improved.^{142,143,144} Some results obtained by its use are given in Table VI.

¹³³ Hfil and Fischer, *J. Am. Chem. Soc.*, **44**, 2582 (1922); Bert and Dorier, *Bull. soc. chim France*, [1] **39**, 1573 (1926).

¹³⁴ Lebeau and Picon, *Compt. rend.*, **156**, 1077 (1913).

¹³⁵ Picon, *Compt. rend.*, (a) **156**, 1181, 1316 (1913); (b) **168**, 894 (1919); (c) **168**, 32 (1919).

¹³⁷ Melnert and Hurd, *J. Am. Chem. Soc.*, **62**, 4540 (1930).

¹³⁸ Hurd and Melnert, *J. Am. Chem. Soc.*, **63**, 259 (1931).

¹³⁹ Kranzfelder and Sowa, *J. Am. Chem. Soc.*, **59**, 1490 (1937).

¹⁴⁰ Campbell and Eby, *J. Am. Chem. Soc.*, **63**, 2683 (1941).

¹⁴¹ See Table VI, note 1, p. 20.

¹⁴² Vaughn, Hession, Vogt, and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

¹⁴³ Nieuwland and Vogt, *The Chemistry of Acetylene*, Chapters II and III, Reinhold Publishing Corp., New York, 1945.

¹⁴⁴ (a) Greenlee, Dissertation, Ohio State University, 1912; (b) Henne and Greenlee, *J. Am. Chem. Soc.*, **65**, 2020 (1943); **67**, 484 (1945).

TABLE VI

1-ALKYNES FROM SODIUM ACETYLIDE AND ALKYL BROMIDES¹⁴

| 1-Alkyne | Yield * % | Reaction time hr. | Moles of Bromide | Moles of HC≡CNa |
|-------------------|--------------|-------------------------|------------------------|--------------------|
| 1-Propyne | 84 † | 5 | 4.25 | 4 |
| 1-Butyne | 89 ‡ | 3 | ‡ | 1 |
| 1-Pentyne | 85 | 5 | 17.1 | 20 |
| 1-Hexyne | 89 | 6½ | 4.5 | 5 |
| 1-Heptyne | 56 | 4 | 2 to 3 | Slight excess |
| | 73 | 6 | 2 to 3 | Slight excess |
| | 83 | 13 | 2 to 3 | Slight excess |
| 5-Methyl-1-hexyne | 68 § | 6 | | 4.5 |
| 1-Octyne | 72 | 22 | 14 | 20 |

* Based on alkyl bromide, which was the limiting factor except as noted.

† A slight excess of methyl bromide was used. The yield based on sodium was 89%.

‡ Diethyl sulfate was used instead of ethyl bromide. The reaction was vigorous so that addition was slow. The yield given is of crude material. Some difficulties were encountered in purification, and some material was lost. The yield of pure product was 65%, but it should be possible to improve this.

§ Insufficient reaction time. The yield was 47% on isooctyl bromide taken, and the recovery of bromide was 31%. The freezing-point curve was poor, probably owing to isomers resulting from impure isooctyl bromide.

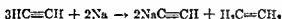
The Preparation of Sodium Acetylide and Other Metallic Acetylides

Sodium acetylide is prepared commonly by passing acetylene into a solution of sodium in liquid ammonia at the boiling point. The reaction is slow because the mechanical difficulty of dissolving a gas in a boiling solution is increased by the vigorous exothermic reaction and consequent dilution of the acetylene by solvent vapors and ethylene.¹⁴ This difficulty has been surmounted most successfully by using a metallic reflux condenser of adequate capacity cooled with Dry Ice.^{13,14a} The acetylene that does not react when first passed through the solution is dissolved and returned to the flask by the condensing ammonia. Excellent directions for this method of preparation have been published.¹⁵ If a suitable condenser is not available, it is probably simplest to introduce a large piece of sodium gradually into a saturated solution of acetylene in liquid ammonia with vigorous stirring as described by Hennion.¹⁶

¹⁴ Greenlee and Henna, *Inorganic Synthesis*, 2, 75 (1946). See also reference 143, Chapter 2, for a discussion of the synthesis of sodium acetylide.

¹⁶ Hennion, *Proc. Indiana Acad. Sci.*, 47, 116 (1935) [*C.A.*, 32, 9039 (1935)].

The addition of a solution of sodium in liquid ammonia to a saturated solution of acetylene in liquid ammonia has been successful,^{142,143} but it is hazardous since the sodium solution cannot be handled in an ordinary separatory funnel. Small amounts of sodium acetylide have been prepared¹³³ by passing acetylene into the sodium solution cooled in Dry Ice. The preparation has also been carried out in an autoclave at room temperature, but there is danger of violent explosions, especially if a trace of air is present.^{142,143} Any of these procedures for preparing sodium acetylide from metallic sodium has two disadvantages: the upper walls of the flask are quickly covered by metallic sodium which is difficult to wash down, and one-third of the acetylene is wasted as ethylene.



A preferable method employing sodium amide in place of sodium was discovered by Picon¹⁴⁷ and developed by others.^{43a,144,145} In practice the method is less troublesome and somewhat more adaptable. The sodium acetylide prepared in this way contains small amounts of iron and other impurities, but these do not appear to interfere with its use in synthesis. In fact the impurities may be beneficial, since it is reported that the acetylide obtained in this way is considerably more reactive than that obtained using sodium.¹⁴⁴ The details of the procedure are given on p. 48.

A reactive form of sodium acetylide has been prepared from acetylene and a suspension of sodium naphthalene in dimethyl ether. The sodium derivatives of other aromatic hydrocarbons can be substituted for sodium naphthalene, and the dimethyl ether can be replaced by ethers of ethylene glycol or of various polyhydroxyl compounds.^{148a}

The acetylides of other alkali and alkaline-earth metals have been prepared but offer no advantages for the synthesis of 1-alkynes.¹⁴⁹ Patents have been issued for the synthesis of mono- and di-substituted acetylenes from calcium carbide and organic halogen or hydroxyl compounds, mostly at high temperatures.^{149a, d, e}

¹⁴² Picon, *Compt. rend.*, **173**, 155 (1921); *Bull. soc. chim. France*, [4] **29**, 709 (1921).

¹⁴³ Hefflbron, Jones, and Weedon, *J. Chem. Soc.*, **1945**, 81.

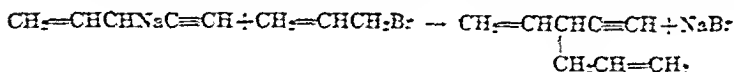
^{144a} Scott, Hansley, and Walker, *J. Am. Chem. Soc.*, **58**, 2442 (1936); U. S. pats. 2,171,867 and 2,171,868 [*C.A.*, **34**, 115, 116 (1940)].

¹⁴⁹ A review of these is given in reference 143, pp. 40-43, 73-79. References dealing especially with their use in alkyne synthesis include: (a) Vaughn and Danehy, *Proc. Indiana Acad. Sci.*, **44**, 144 (1934) [*C.A.*, **30**, 429 (1936)]; (b) Campbell and Campbell, *Proc. Indiana Acad. Sci.*, **50**, 123 (1940) [*C.A.*, **35**, 5457 (1941)]; (c) Soc. pour l'ind. chim. à Bale, Brit. pat. 293,090 [*C.A.*, **23**, 2723 (1929)]; (d) Dutt, Fr. pat. 677,338 [*C.A.*, **24**, 2956 (1930)]; (e) Corson, Brit. pat. 279,095 [*C.A.*, **22**, 2755 (1928)]; Fr. pat. 642,170 [*C.A.*, **23**, 1135 (1929)].

The Alkylation of Sodium Acetylide

The alkylation of sodium acetylide by alkyl halides is limited to the introduction of primary alkyl groups, RCH_2CH_2- . Secondary and tertiary halides and primary halides with branching on the second carbon, R_2CHCH_2- , give only traces of 1-alkyne; the principal product is the alkene formed by dehydrohalogenation.^{12,13} The reactivity of the alkyl halides with sodium acetylide increases with the atomic weight of the halogen and decreases with increasing size of the alkyl group. Methyl chloride gives propyne in 54% yield in sixteen hours, all the halide being used, but *n*-butyl chloride yields only 30% of 1-hexyne after twenty-five hours.¹⁴ Aryl halides cannot be employed; they either fail to react (chlorobenzene) or undergo ammonolysis only (*o*-chloronitrobenzene).¹⁵ Products other than 1-alkynes are obtained with vinyl chloride,¹⁶ 1-bromo-1-butyne,¹⁴ and chloromethyl ether.¹⁴ Yields of 60-75% of ethers of 3-butyne-1-ol have been obtained from a number of ethers of ethylene bromohydrin $\text{ROCH}_2\text{CH}_2\text{Br}$.¹⁷ Ethylene bromohydrin gives mainly acetaldehyde.¹⁸

Allyl halides react with sodium acetylide^{14,19} to give a mixture of unidentified compounds containing eight and eleven carbon atoms. This anomalous result is attributed to metalation of the methylene group of 1-penten-



4-yne. The eleven-carbon compound $\text{CH}_2=\text{CHC}(\text{CH}_2\text{CH}=\text{CH}_2)_2$ would be formed from $\text{CH}_2=\text{CH}-\text{CHCH}_2\text{CH}=\text{CH}_2$ by further reac-

tion with sodium acetylide and allyl bromide. Analogous products were obtained from methallyl chloride.¹⁴

Alkyl bromides, especially if pure, give the best results, since they are more reactive than chlorides yet produce smaller amounts of amines than the iodides. The synthesis has been carried out in an autoclave at higher pressures and temperatures,^{12,14,20,21} but, except with

¹² Picot, *Compt. rend.*, 168, 825 (1919).

¹³ McCusker and Kroege, *J. Am. Chem. Soc.*, 59, 213 (1937).

¹⁴ Lespièze and Journaud, *Bull. soc. chim. France*, [4] 49, 423 (1931).

chlorides, the best results are obtained at atmospheric pressure at the boiling point of liquid ammonia.

The chlorides and even the bromides are not readily separated from the alkynes, and efficient fractionating columns must be used in purifying the products. A column of 25-plate efficiency gives 1-heptyne and 1-octyne of high purity.^{142,143} No satisfactory chemical method of removing the halogen compound has been discovered.^{142,143} A large excess of sodium acetylide is ineffective in reducing the amount of the impurity, but with very efficient stirring less halide is found in the product.

The yields are lowered by entrainment and vaporization of the alkyne during the addition of water to the liquid ammonia solution at the end of the reaction unless adequate precautions are taken, such as the use of an efficient Dry Ice-cooled condenser^{142,144} (p. 48). The removal of the ammonia before hydrolysis is not advisable, for the hot concentrated sodium hydroxide produced on addition of water may then rearrange the 1-alkyne. Thus, in the reaction of butyl bromide and sodium acetylide, removal of ammonia followed by addition of water gave a product boiling at 71–72° containing only 79% of 1-hexyne.¹⁴⁴

Organic solvents do not improve the yield in the synthesis and are often detrimental, although small amounts of ether may increase the rate of reaction slightly. The yields are not altered by substitution of cadmium, aluminum, or iron containers for the usual glass flask; stirrers of Monel metal, nickel, Nichrome, brass, and glass have been used.

The application of the liquid ammonia method to dihalides has been successful.^{144,145} 1,6-Heptadiyne and 1,8-nonadiyne are obtained without difficulty from trimethylene and pentamethylene bromides in 40–43% and 84% yields, respectively.¹⁴⁴ The crude yield of the former is 70–74%, but 13% of low-boiling material, possibly 2-penten-4-yne, is present, and the product is difficult to purify on account of polymerization. 1-Bromo-3-chloropropane gives a 57% yield of 5-chloro-1-pentyne.¹⁴⁴ Compounds having halogens on adjacent carbon atoms usually undergo dehydrohalogenation,^{142,143,144} and methylene chloride gives unidentified material.¹⁴⁴

Alkyl sulfates may be used in the alkylation instead of halides^{137,138} and are superior for the synthesis of propyne and 1-butyne.^{140,141} It should be remembered that only one of the alkyl groups in an alkyl

¹⁴² The physical constants of the pure alkynes are given in references 140 and 144. They are also given in *Selected Values of Properties of Hydrocarbons*, American Petroleum Institute Research Project 44, National Bureau of Standards, Washington, D. C.

¹⁴³ See the private communication from Hurd cited by Vaughn, Hennon, Vogt, and Nieuwland, *J. Org. Chem.*, **2**, 11 (1937).

¹⁴⁴ Lespieau and Journaud, *Compt. rend.*, **158**, 1410 (1929).

sulfate reacts. It is noteworthy that diisopropyl sulfate gives 29–50% yields of isopropylacetylene.¹³⁹

The methyl, propyl, and butyl esters of *p*-toluenesulfonic acid will alkylate sodium acetylide in liquid ammonia in 37–47% yields, but solid esters such as the amyl cannot be used.¹³⁹ No alkylation is obtained with tributyl phosphate, amyl acetate, or butyl acetate.

Sodium acetylide, prepared from acetylene and sodium naphthalene in a suitable ether solvent, furnishes propiolic acid in 69% yield on carbonation and is reported to undergo alkylation with alkyl halides.^{142a}

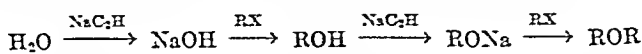
Side Reactions in the Alkylation of Sodium Acetylide

The by-products in this alkylation reaction are as follows: olefins, amines, ethers, alcohols, disubstituted acetylenes, and acetylene.

Olefins. As mentioned above, secondary and tertiary alkyl halides, and primary alkyl halides branched on the second carbon, give mainly dehydrohalogenation to olefins in the alkylation reaction. When carefully purified primary bromides, RCH_2CH_2Br , are used this olefin formation is unimportant.¹⁴⁴ The alkenes may arise in part as a result of the action of the alkyl halides with sodium amide, sodium hydroxide, or sodium alkoxides present in low concentration, but sodium acetylide is a strong base and might be expected to cause some dehydrohalogenation. Since the olefins have two fewer carbons than the desired acetylenes the separation is not difficult.

Amines. The reaction of ethyl bromide or iodide with liquid ammonia to produce a mixture of ethyl amines¹⁵⁶ has been found^{142, 143} to represent a general reaction of alkyl halides and to occur in 1-alkyne syntheses. Iodides react most readily and chlorides least. The amines obtained as by-products in the acetylene preparation consist of about equal parts of primary and secondary with variable amounts of tertiary. At atmospheric pressure and 34° this side reaction is unimportant with bromides, but at high pressures and temperatures it is significant. Alkyl sulfates give higher yields of amines as by-products.

Ethers and Alcohols. The presence of moisture may result in the formation of ethers and alcohols by the following reaction.



The Williamson synthesis of ethers has been shown to proceed smoothly in liquid ammonia.¹⁵⁷ Alcohols may also be present as impurities in the

¹⁵⁶ Picon, *Bull. soc. chim. France*, [4] 35, 979 (1924).

¹⁵⁷ Vaughn, Vogt, and Nieuwland, *J. Am. Chem. Soc.*, 57, 510 (1935).

alkyl halides and lead to ether formation.¹⁴⁴ Ethers were isolated in 1% to 5% yields by fractionation of the residues from the distillation of 1-alkynes,^{142,143} and alcohols were ordinarily present in amounts less than 1%. Pure bromides give no significant quantities of ethers although commercial bromides sometimes give several per cent.

Disubstituted Acetylenes. A small amount of disubstituted acetylene usually can be isolated from the reaction of sodium acetylide with an alkyl halide in liquid ammonia. When butyl and amyl bromides are used, 2-3% and occasionally up to 30% of dialkylacetylenes may be formed.^{142,143} Much less of these by-products has been reported by others,¹⁴⁴ and it has been suggested they arise from the presence of sodium carbide. The presence of sodium carbide in metallic acetylides prepared in liquid ammonia is disputed.^{154,155} Certain results^{144,145} suggest that an equilibrium exists between sodium acetylide and sodium carbide.



Such an equilibrium is well established for the Grignard reagent from acetylene (p. 32).

Acetylene. Some acetylene usually is produced in the final stages of this synthesis,¹⁴⁶ but it is readily removed if the product is properly fractionated.

Other Impurities. The following have been listed^{142,143} as possible by-products: rearranged hydrocarbons resulting from the action of strong bases such as sodium acetylide, dimethylethynylcarbinol from incomplete removal of acetone from the acetylene, peroxides produced by the action of air or sodium peroxide, and polymers. A small amount of polymerization usually occurs when the higher-boiling alkynes are distilled. These side reactions are ordinarily unimportant, although the rapidity with which the physical constants of acetylenes are changed by peroxide formation on exposure to air has been stressed.^{112,113,153}

Acetylene Mono- and Di-magnesium Bromide

Acetylenemagnesium bromide and acetylenedimagnesium bromide have been used in the synthesis of many acetylenic compounds. A mixture of these which behaves mainly as the dimagnesium derivative was first prepared by Iozitsch¹⁵¹ and is easily obtained at ordinary

¹⁴² Moissan, *Compt. rend.*, **127**, 911 (1898).

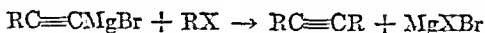
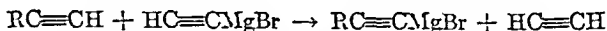
¹⁴³ See reference 142, p. 17, and 143, pp. 41, 44.

¹⁴⁴ Heisig and Hurd, *J. Am. Chem. Soc.*, **55**, 3485 (1933).

¹⁵¹ The extensive work of Iozitsch is noteworthy: *J. Russ. Phys. Chem. Soc.*, **34**, 242 (1902); **35**, 431, 1269 (1903); **38**, 252, 656 (1906); *Bull. soc. chim. France*, [3] **30**, 210 (1903). [3] **32**, 552 (1904); [3] **34**, 181 (1905); [4] **4**, 981, 1203 (1908).

pressures;¹⁶² its reactions with many carbonyl compounds have been studied. The proportion of monomagnesium derivative in the mixture is influenced by the amount of acetylene, but even when excess acetylene is present some glycol is produced in the reaction with an aldehyde.^{161, 163} By using excess acetylene under pressure with efficient stirring it is possible to obtain a solution which behaves mainly as the monomagnesium derivative.^{164, 165} The preparation of such a reagent using a shaking machine has been described.¹⁶⁶ The reaction between acetylene and ethylmagnesium bromide is allowed to proceed at ordinary pressure and temperature until ethane is no longer evolved (seven to eight hours), and the reaction is completed by several hours' stirring and refluxing under acetylene pressure of half an atmosphere. On carbonation this solution gives a 62% yield of propiolic acid and a 10% yield of acetylenedicarboxylic acid.¹⁶⁴ The reaction has been improved so that an 87% yield of propiolic acid can be obtained.¹⁶⁵

The composition of the Grignard solution prepared at atmospheric pressure has been investigated.¹⁶⁷ It is not safe to estimate the proportions of mono- and di-magnesium derivatives present from the amounts of mono- and di-substituted acetylenes obtained in alkylation or addition reactions because the following reactions can also account for disubstituted compounds.



The alkylation of the Grignard reagent of acetylene has not been studied extensively, although it appears to give rather satisfactory yields of 1-alkynes under the special conditions already mentioned.^{164, 165} Benzyl bromide gives a 70% yield of 3-phenylpropyne, 8% of 1,4-di-

¹⁶² Wieland and Kloss, *Ann.*, **470**, 201 (1929), have described the preparation and use of such a solution.

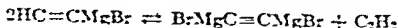
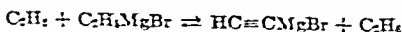
¹⁶³ Oddo, *Atti. accad. naz. Lincei*, [5] **13**, II, 187 (1904) (*Chem. Zentr.*, 1904, II, 943); *Gazz. chim. ital.*, **34**, II, 429 (1904); **38**, I, 625 (1908).

¹⁶⁴ Grignard, Lapayre, and Tchéoufaki, *Compt. rend.*, **187**, 517 (1928).

¹⁶⁵ Tchéoufaki, *Contrib. Inst. Chem. Natl. Acad. Peiping*, **1**, 127 (1934) [*C.A.*, **29**, 2513 (1935)].

¹⁶⁶ Dane, Höss, Bindseil, and Schmitt, *Ann.*, **532**, 39 (1937).

¹⁶⁷ Zalkind and Rosenfeld, *Ber.*, **57**, 1620 (1924); Kleinfeller and Lohmann, *Ber.*, **71**, 2608 (1938). The latter workers used a kinetic method and concluded that, contrary to common belief, the monomagnesium derivative is formed first. The following reactions account for their results.



phenyl-2-butyne, and 12% of acetylene, while butyl bromide produces 72% of 1-hexyne. The solution obtained when only 1 mole of acetylene has been absorbed in 1 mole of ethyl- or phenyl-magnesium bromide produces 39% of 1-hexyne and 30% of 5-decyne by reaction with butyl bromide and only 20% of 3-hexyne with ethyl bromide. The reactions with butyl bromide are carried out at 80-90°. When the acetylenic Grignard reagent is prepared by the procedure of Iozitsch¹⁶¹ and allowed to react with primary alkyl halides, the products include saturated hydrocarbons and olefins as well as disubstituted acetylenes which are produced in low yields only.¹⁶² Butyl bromide gives C_4H_{10} , C_4H_8 , a polymer of the latter, and a little 5-decyne. Isoamyl bromide behaves similarly, but no 9-octadecyne is isolated when *n*-octyl bromide is used. No 1-alkynes were reported. Wiefand and Kloss¹⁶² obtained only disubstituted acetylenes under comparable conditions from benzohydryl chloride and triphenylmethyl chloride.

The reaction of allyl bromide with the monobromomagnesium reagent was reported to give allylacetylene in 75% yield,¹⁶⁴ but this result could not be duplicated.¹⁶⁵ The reaction of allyl bromide with alkylacetylenic Grignard reagents occurs only in the presence of catalysts such as cuprous or cupric salts (p. 34).¹⁷⁰ These catalysts have not been tried with the Grignard reagent from acetylene.

THE SYNTHESIS OF DISUBSTITUTED ACETYLENES

The synthesis of pure disubstituted acetylenes with two aliphatic groups attached to the triple bond cannot be accomplished by the usual dehydrohalogenating agents since these reagents cause a rearrangement of the acetylenic linkage. Such compounds are best prepared from metallic derivatives of acetylenes and alkyl halides in liquid ammonia or alkyl sulfates in ether or other solvents.

Alkylation in Organic Solvents. Nef¹⁷¹ reported the methylation of phenylacetylene by heating it with methyl iodide and potassium hydroxide, and Morgan¹⁷² obtained 1-phenyl-1-butyne by ethylating sodium phenylacetylide with ethyl iodide. Both reactions were carried out in sealed tubes at about 140°, and low yields resulted. Except in liquid ammonia, the sodium derivatives of acetylenes are remarkably inert toward alkyl halides, and vigorous, deep-seated decomposition

¹⁶¹ Malinovskii and Fedoseev, *Trudy Gor'kov Gosudarst. Pedagog. Inst.*, 1940, No. 5, 43; *Khim. Referat. Zhur.*, 4, No. 2, 40 (1941) [*C.A.*, 37, 3048 (1943)].

¹⁶² Grignard and Lapayre, *Compt. rend.*, 192, 250 (1931).

¹⁷⁰ Danehy, Killian, and Nieuwland, *J. Am. Chem. Soc.*, 55, 611 (1936).

¹⁷¹ Nef, *Ann.*, 310, 333 (1900).

occurs at temperatures sufficiently high to bring about a reaction.¹⁷² Silver, cuprous, and mercuric acetylides are also inert toward alkyl halides.

Acetylenic Grignard reagents are less reactive than alkyl- or aryl-bromomagnesium compounds as measured by their tendency to add to benzonitrile,¹⁷³ and the reaction of these reagents with saturated aliphatic halides is without synthetic value, although very low yields of dialkylethyne from alkynylmagnesium bromides and tertiary alkyl halides have been reported.¹⁷⁴ The yield of 3,3-dimethyl-4-nonyne from hexynylmagnesium bromide and *tert*-amyl bromide was only 3%. With more reactive halides the synthetic results are better. Phenylethyneylmagnesium bromide reacts with triphenylmethyl chloride,¹⁷⁵ benzohydril bromide,¹⁷² and α -furfuryl chloride¹⁷⁵ to give satisfactory yields of the expected disubstituted acetylenes. Its reaction with allyl bromide to form 1-phenyl-4-penten-1-yne, $C_6H_5C\equiv CCH_2CH=CH_2$, in 70% yield has been described^{173,176} but could be duplicated¹⁷⁰ only in the presence of catalysts such as cuprous or cupric halides or cuprous cyanide. Alkynylmagnesium bromides failed to react with allyl bromide on standing with frequent stirring for twenty-three days or by refluxing for two to twelve hours in benzene or di-*n*-amyl ether without catalysts. Cuprous chloride and bromide are the best catalysts, giving high yields of the enyne $RC\equiv CCH_2CH=CH_2$ with *n*-amyl-, *n*-butyl-, phenyl-, and vinyl-ethynylmagnesium bromides. 1-Octen-4-yne is readily formed from allyl chloride and pentynylmagnesium bromide in the presence of cuprous salts.¹⁷⁴ It has been suggested that the difference in the results of the earlier and later investigators might have been due to impurities in the magnesium in the initial experiments. These catalysts are not effective in promoting a reaction between acetylenic Grignard reagents and alkyl halides of normal reactivity.¹⁷⁰ However, methylene iodide and phenylethyneylmagnesium bromide were reported to give an 8% yield of 1,5-diphenyl-1,4-pentadiyne,¹⁷⁶ $C_6H_5C\equiv CCH_2C\equiv CC_6H_5$, but methylene bromide failed to react.¹⁷⁷ Likewise, chloromethyl ethers and chloromethyl esters were unreactive¹⁷⁷ either with acetylenic Grignard reagents or with the sodium derivatives.

In the preparation of Grignard reagents from monosubstituted acetylenes, ethylmagnesium bromide appears to be superior to methylmagnesium iodide; the use of 3 moles of ether for each mole of metallic

¹⁷² Johnson, Schwartz, and Jacobs, *J. Am. Chem. Soc.*, **60**, 1882 (1938).

¹⁷³ Gilman, St. John, St. John, and Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1936).

¹⁷⁴ Campbell and Eby, *J. Am. Chem. Soc.*, **62**, 1798 (1940).

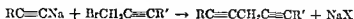
¹⁷⁵ Gilman, Van Ess, and Burtner, *J. Am. Chem. Soc.*, **55**, 3461 (1933).

¹⁷⁶ Grignard and Lapayre, *Bull. soc. chim. France*, [4] **43**, 141 (1928).

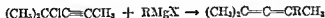
¹⁷⁷ Hennion and Bell, *J. Am. Chem. Soc.*, **65**, 1847 (1943).

derivative has been recommended.¹⁷³ Phenylmagnesium bromide is also satisfactory, but since no gas is evolved the course of the reaction is less easily followed.

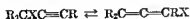
1,4-Diynes have been prepared by the reaction of substituted propargyl bromides and sodium alkynides at 140°.¹⁷⁹ Although the corre-



sponding acetylenic Grignard reagents fail to react on boiling for six hours in toluene, the use of catalysts¹⁷⁹ might make this reaction successful. The yields are only 15–20% even though the bromo compounds react to the extent of 80–90%. By-products include polymers and tri- and tetra-acetylenes, for the central methylene group is sufficiently acidic to form sodium derivatives ($\text{RC}\equiv\text{CCHNaC}\equiv\text{CR}'$) that may react with part of the bromide. Attempts to prepare aryl-aliphatic or diaryl-1,4-diacetylenes failed, and only polymers resulted.¹⁷⁹ The saturated Grignard reagents, on the other hand, were reported to give at ordinary temperatures almost quantitative yields of disubstituted acetylenes with propargyl bromides of the type $\text{RC}\equiv\text{CCH}_2\text{Br}$; the synthesis of 4-decyne from 1-bromo-2-octyne and ethylmagnesium bromide was cited as an example.¹⁷⁹ The yield of benzylphenylacetylene by this procedure was only 27%.⁸³ The method has been used to prepare 4-octyne from ethylmagnesium bromide and 1,4-dibromo-2-butyne.^{180a} It has also been applied to tertiary propargyl chlorides $\text{RC}\equiv\text{CC}(\text{R}'\text{R}'')\text{Cl}$, which react with concentrated Grignard solutions at 60–80° to give the disubstituted acetylenes in 60–74% yields.¹⁷⁴ Although some care was taken to establish the carbon skeletons of these acetylenes, similar reactants have more recently been reported to give allenes in fair yields.^{180b} An allylic rearrangement of the halogen of the propargyl



halide may also complicate the synthesis at earlier stages.^{180c}



1,5-Diacetylenes may be prepared by coupling two molecules of substituted propargyl bromide using magnesium or sodium, magnesium giving 50–60% yields.¹⁸¹ If excess sodium is used some reduction occurs

¹⁷³ Tehao Yin Lai, *Bull. soc. chim. France*, [4] 53, 682 (1933).

¹⁷⁹ Tehao Yin Lai, *Bull. soc. chim. France*, [4] 53, 1533, 1537 (1933).

^{180a} Johnson, *J. Chem. Soc.*, 1946, 1009.

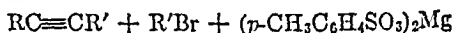
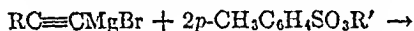
^{180b} Zakhareva, *J. Gen. Chem. U.S.S.R.*, 17, 1277 (1947) [*C.A.*, 42, 3722 (1948)].

^{180c} Johnson, *The Chemistry of the Acetylenic Compounds*, Vol. I, The Acetylenic Alcohols, Edward Arnold and Co., 1946, p. 63.

¹⁸¹ Tehao Yin Lai, *Bull. soc. chim. France*, [4] 53, 1543 (1933).

to a γ -eneyne. Sodium amide polymerizes these diynes, presumably by first rearranging them to β -diynes.

The alkylation of alkyl or aryl acetylenes by alkyl sulfates or sulfonates in ether or high-boiling inert solvents is an excellent synthetic method for preparing disubstituted acetylenes. Gilman and Beaber¹⁵² appear to have been the first to apply this reaction when they prepared 4-chloro-1-phenyl-1-butyne, ($\text{C}_6\text{H}_5\text{C}\equiv\text{CCH}_2\text{CH}_2\text{Cl}$), by interaction of phenylethynylmagnesium bromide and β -chloroethyl *p*-toluenesulfonate. A number of monosubstituted acetylenes have been methylated in about 80% yield by treating the sodium derivatives with excess dimethyl sulfate.²³ These yields are based on the unrecovered alkyne. Various esters of aromatic sulfonic acids react readily with sodium alkynides or acetylenic Grignard reagents^{93, 172, 183} in ether, tetralin, or mineral oil. It is often advantageous to substitute dibutyl ether or toluene for diethyl ether as the solvent. The bromomagnesium alkynide has the disadvantage that two moles of the sulfonic ester are necessary. The



reaction of phenylethynylsodium with benzyl or β -chloroethyl *p*-toluenesulfonate fails to give benzylphenylacetylene or β -chloroethylphenylacetylene, although these compounds are readily prepared using phenylethynylmagnesium bromides.^{93, 172}

The very sensitive phenoxyethynylmagnesium bromide gives satisfactory yields of 1-phenoxyhexyne with butyl *p*-toluenesulfonate, but the yield of 1-phenoxybutyne with ethyl *p*-toluenesulfonate is low.^{15b} Disubstituted acetylenes have been prepared in good yield by the reaction of acetylenic Grignard reagents with alkyl sulfates in ether.¹⁵⁴ Table VII summarizes the synthetic data on disubstituted acetylenes prepared by these methods.

Alkylations in Liquid Ammonia. The first alkylation of the sodium derivative of a monosubstituted acetylene in liquid ammonia was carried out by Heisig,^{10 & 155} who treated propynylsodium with methyl iodide or dimethyl sulfate. Alkyl sulfates, sulfonates, and bromides were used for alkylation of vinyl ethynylsodium in liquid ammonia.¹⁵⁶ The yields were moderate except with heptyl bromide, which gave 80% of 1-heptyl-2-vinylacetylene. Propyl-, butyl-, amyl-, and phenyl-ethynylsodium

¹⁵² Gilman and Beaber, *J. Am. Chem. Soc.*, **45**, 839 (1923).

¹⁵³ Truchet, *Ann. chim.*, [10] **16**, 309 (1931).

¹⁵⁴ Thorn, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 796 (1936).

¹⁵⁵ Heisig, *J. Am. Chem. Soc.*, **53**, 3245 (1931).

¹⁵⁶ Jacobson and Carothers, *J. Am. Chem. Soc.*, **55**, 1622 (1933).

TABLE VII

DISUBSTITUTED ACETYLENES PREPARED BY VARIOUS METHODS

| Acetylene | Solvent * | Yield † % | Method ‡ | Reference |
|------------------------------------|---------------|--------------|----------|-----------|
| 4-Methyl-2-pentyne | Ether | 28 | 1 | 36 |
| 2-Heptyne | Ether | 8 | 1 | 184 |
| 2-Methyl-3-hexyne | Ether | 39 | 1 | 35, 36 |
| 4,4-Dimethyl-2-pentyne | Ether | 55 | 2 | 117a |
| 2-Octyne | Ether | 81 | 2 | 28 |
| 3-Octyne | Ether | 70 | 1 | 184 |
| 2-Nonyne | Ether | 8 | 1 | 184 |
| | Ether | 79 | 2 | 28 |
| | Tetralin | 33 | 4 | 183 |
| 3-Nonyne | Ether | 8 | 1 | 184 |
| | Tetralin | 50 | 4 | 183 |
| | Vaseline oil | 47 | 4 | 183 |
| 3-Decyne | Tetralin | | 4 | 183 |
| 4-Decyne | Vaseline oil | 70 | 4 | 183 |
| 5-Undecyne | Dibutyl ether | 63 | 4 | 172 |
| 3-Dodecyne | Benzene | 23 | 4 | 183 |
| 6-Dodecyne | Dibutyl ether | 65 | 4 | 172 |
| 1-Chloro-4-tridecyne | Ether | 8 | 1 | 184 |
| 1-Hexen-3-yne | Ether | 13 | 1 | 177 |
| 5,8-Tridecadiyne | Ether | 83 | 2 | 28 |
| 1-Cyclohexyl-2-butyne | Ether | 83 | 2 | 28 |
| 5-Cyclohexyl-2-pentyne | Ether | 80 | 2 | 28 |
| 6-Cyclohexyl-2-hexyne | Tetralin | 44 | 4 | 183 |
| 1-Phenyl-1-propyne | Benzene | 56 | 4 | 183 |
| 1-Phenyl-1-butyne | Dibutyl ether | 77 | 4 | 172 |
| 1-Phenyl-4-chloro-1-butyne | Ether | 45-75 | 3 | 182, 172 |
| 1-Phenyl-1-pentyne | Vaseline oil | 65 | 4 | 183 |
| 1-Phenyl-5-chloro-1-pentyne | Dibutyl ether | 75 | 4 | 172 |
| 1-Phenyl-1-hexyne | Vaseline oil | 57 | 4 | 183 |
| | Toluene | 65-70 | 4 | 172 |
| 1,3-Diphenylpropyne | Ether | 72 | 3 | 93 |
| 1-p-Bromophenyl-3-phenyl-1-propyne | Ether | 26 | 3 | 93 |
| 3-p-Bromophenyl-1-phenyl-1-propyne | Ether | 50 | 3 | 93 |
| 1-Phenoxy-1-butyne | Ether | 15 | 3 | 185 |
| 1-Phenoxy-1-hexyne | Ether | 52 | 3 | 185 |

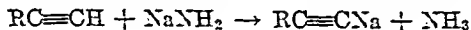
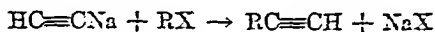
* The sodium derivatives were usually prepared in ether and the higher-boiling solvent was added for the last part of the reaction only. The acetylide can be prepared in toluene and probably in other solvents if the temperature is maintained at 35-40°, but at higher temperatures the derivative is gelatinous and difficult to stir.

† S indicates that the yield was reported as satisfactory.

‡ Methods. (1) Grignard reagent and sulfate; (2) sodium alkynide and sulfate; (3) Grignard reagent and sulfonate; (4) sodium alkynide and sulfonate.

were alkylated with a variety of alkyl halides and sulfates.^{142, 143} Bromides were reported to be the most effective alkylating agents, followed by iodides, sulfates, and chlorides in that order. The molecular weight of the alkyl group did not appear to influence the yield in the narrow range studied. The yields using bromides were between 42% and 58%, and the reaction could be carried out at atmospheric pressure or in an autoclave.

The preparation of a 1-alkyne from an alkyl halide and sodium acetylide, its conversion to an alkynylsodium with sodium amide, and the reaction of this derivative with alkyl halide to give a disubstituted acetylene can be conducted successively in one liquid ammonia solution to yield dialkylethyne in excellent yields and with saving of time.¹⁵⁷ The success of this method was attributed to the greater solubility of sodium acetylide relative to sodium amide and to the greater reactivity of 1-alkynes towards sodium amide. For symmetrical acetylenes it is sufficient to mix sodium acetylide, sodium amide, and alkyl halide in the molar ratio 1:1:2 with vigorous stirring. The following reactions take place.



Bromides are the most satisfactory alkylating agents at atmospheric pressure, and chlorides give only low yields. Chlorides are more effective in an autoclave, but without stirring the yields remain lower than from bromides at ordinary pressures.

Unsymmetrical acetylenes can also be produced without the isolation of the intermediate 1-alkynes by adding an alkyl bromide to sodium acetylide in liquid ammonia, treating the solution after some time with a liquid ammonia suspension of sodium amide, and finally adding the second alkyl halide.

These methods are limited to alkyl halides of moderate molecular weight.¹⁵³ With *n*-octyl bromide the yield of 9-octadecyne, $\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{C}(\text{CH}_2)_7\text{CH}_3$, is only 15%, although 75% of 1-decyne, $\text{CH}_3(\text{CH}_2)_7\text{C}\equiv\text{CH}$, is also produced. The yield of 9-octadecyne increases to 27% at 8 atmospheres and only 15% of 1-decyne is isolated. Decyl bromide gives only decylamine and 1-dodecyne at atmospheric or higher pressures.

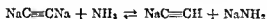
The introduction of a heavier alkyl radical first has been sug-

¹⁴² Bried and Hession, *J. Am. Chem. Soc.*, **59**, 1310 (1937).

¹⁴³ Bried and Hession, *J. Am. Chem. Soc.*, **60**, 1717 (1938).

gested,¹⁴⁴ and several new disubstituted acetylenes have been prepared in this way.

The use of two liquid ammonia condensers¹³⁹ mounted one above the other has been proposed.¹³⁷ A metal condenser cooled with Dry Ice¹³⁸ is more effective and enables one to avoid the troublesome transfer of the sodium amide in liquid ammonia by passing into such a suspension just half enough acetylene to convert it to sodium acetylide. The resulting mixture is probably disodium acetylide ammonolyzed to an unknown extent. A simplified two-step process for preparing disubstituted



acetylenes in which the intermediate 1-alkyne is dried but not purified after hydrolysis, and is converted to the alkynide by addition to sodium amide in liquid ammonia, has been devised.¹⁴⁴

Table VIII summarizes the more recent results on the synthesis of disubstituted acetylenes by these methods.

Sodium amide is superior to metallic sodium for the formation of sodium alkynides in liquid ammonia as it is for the formation of sodium acetylide (p. 27). The reduction of higher acetylenes to olefins by the metal¹³⁰ has been observed. The report that the hydrogenation^{142,143} is less extensive than with acetylene has not been confirmed in other laboratories.^{144,150} Some reduction also occurs when sodium is used to form acetylides in inert solvents such as ether,¹⁵¹ but this side reaction is less important here than in liquid ammonia. The use of sodium amide in inert solvents has been recommended because the reaction is more rapid and there is no danger of hydrogenation.²⁸ Furthermore, it is difficult to accomplish a complete removal of the metallic sodium because of the tendency of some of the derivatives to form a protective coating on the metal. The quality of the sodium amide is an important consideration (p. 9).

Sodium derivatives have been prepared in liquid ammonia, this solvent being replaced with benzene, toluene, or ether before alkylating;¹⁷⁷ this procedure appears to offer no special advantages.

Acetylenic Grignard reagents can be alkylated in low yield in liquid ammonia solution.¹⁵²

¹³⁷ Vaughn and Pozzi, *J. Chem. Educ.*, **8**, 2433 (1931).

¹³⁸ Lebeau and Picon, *Compt. rend.*, **157**, 137, 223 (1913). It was reported that phenylacetylene gave ethylbenzene.

¹⁴¹ (a) Lagermark and Eltekov, *J. Russ. Phys. Chem. Soc.*, **11**, 125 (1879); *Ber.*, **12**, 854 (1879); (b) Favorskii, *J. Russ. Phys. Chem. Soc.*, **19**, 553 (1887) [*Chem. Zentr.*, **19**, 242 (1888)]; (c) Moureu and Delange, *Bull. soc. chim. France*, [3] **25**, 302 (1901); (d) Fuson and Meek, *J. Org. Chem.*, **10**, 551 (1945).

¹⁵² Hennion and Wolf, *Proc. Indiana Acad. Sci.*, **43**, 93 (1939) [*C.A.*, **33**, 6794 (1939)].

TABLE VIII

DISUBSTITUTED ACETYLENES PREPARED IN LIQUID AMMONIA

| Disubstituted Acetylene | Yield * % | Reference | Disubstituted Acetylene | Yield * % | Reference |
|-------------------------|--------------|-------------------|-------------------------|--------------|-----------|
| 2-Butyne | 36 | 10b, 185, 144 | 7-Methyl-3-octyne | 35 | 54 |
| 2-Pentyne † | 59 | 144 | 5-Decyne | 69 | 140, 187 |
| 2-Hexyne | — | 140 | 8-Methyl-4-nonyne | 35 | 54 |
| 3-Hexyne ‡ | 75 | 144, 140, 187 | 5-Undecyne | 60 | 54 |
| 2-Octyne § | 58 | 144, 140 | 6-Dodecyne | 30 | 187 |
| 3-Octyne | 64 | 144, 140, 187 | 7-Tetradecyne | 38 | 188 |
| 4-Octyne | 60-66 | 54, 144, 140, 187 | 9-Octadecyne | 15-27 | 188 |
| 4-Octyne ¶ | 81 | 144, 54 | 1-Phenylpropyne †† | 50 | 54 |
| 3-Nonyne ** | 35 | 54 | 2,7-Nonadiyne ‡‡ | 76 | 144 |

* Based on alkyl bromides. When two different halides were used the yield was based on the heavier, which was introduced first. The one-step process was used except as noted.

† Two-step process using dimethyl sulfate first and transferring the propyne and ammonia as a gas to the second flask containing sodium amide in liquid ammonia.

‡ This is the only experiment employing the new technique of metering into a sodium amide suspension just half as many moles of acetylene. Bried and Hennion, ref. 187, obtained only 47% by the standard one-step method. Using diethyl sulfate the yield was 37% but the product was unusually pure (ref. 144).

§ Two-step process. Yield based on 1-heptyne and allowing twelve hours. Recovery of 1-heptyne was 20%. A longer reaction time was recommended. Using 1-propyne and amyl bromide the yield was 56% and the 2-octyne was very difficult to separate from the bromide.

|| In the simplified two-step process a yield of 67% was obtained and 16% of 1-hexyne was isolated (ref. 144).

¶ Two-step process.

** The two-step process gave a 54% yield (ref. 142).

†† Based on phenylacetylene. Dimethyl sulfate was used. A yield of 43% was reported using methyl iodide (ref. 142).

‡‡ Based on 1,6-heptadiyne; 3% was recovered and 5% of 1,6-octadiyne was isolated.

THE SYNTHESIS OF DIARYLACETYLENES (TOLANS)

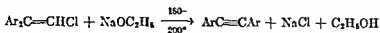
Tolan and substituted tolans appear to be very readily formed, and various special methods have been found for their preparation. The standard synthesis from stilbene dibromide and ethanolic potassium hydroxide has been modified many times between the first report in 1868¹³ and the modern version of 1942.⁵ Tolans have been synthesized in 75% yield by a neat but expensive method which involves the oxidation of benzil dihydrazone with yellow mercuric oxide.¹⁴ There appears to be no possibility of the formation of stilbene in this preparation, which

¹³ Limpricht and Schwanert, *Ann.*, 145, 330 (1868).

¹⁴ Curtius and Thun, *J. prakt. Chem.*, [2] 44, 171 (1891); Schlenk, Bergmann, and Rodloff, *Ann.*, 463, 76 (1925).

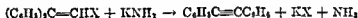
is an advantage when high purity is paramount since stilbene and tolan form a solid solution *not readily separable*.¹⁸⁵ Di-*p*-tolylacetylene¹⁸⁶ and α -naphthylphenylacetylene¹⁸⁷ were prepared by the same method in very high yields.¹⁸⁸

The preparation of diphenylacetylenes by the dehydrohalogenation and rearrangement of unsymmetrical diarylhaloethylenes or ethanes was first reported in 1894.¹⁸⁸ The yield of tolan from diphenylchloro-



ethylene was only 9%, the principal product being 2,2-diphenylvinyl ethyl ether. The yields of di-*p*-tolylacetylene and of di-*p*-anisylacetylene from the corresponding chlorides were 85% and 55%, respectively. A disadvantage of the method is the necessity of using a sealed tube for the reaction. The starting materials are prepared in good yields by condensing dichloroacetal with benzene, toluene, or anisole and removing hydrogen chloride from the resulting 1,1-diaryl-2,2-dichloroethane by ethanolic potassium hydroxide. Potassium amyloxide was used to prepare 3,4,3',4'-tetramethoxytolan from 1,1-bis-(3,4-dimethoxyphenyl)-2-chloroethylene.¹⁸⁹

When potassium amide in liquid ammonia was substituted for the ethanolic sodium ethoxide in this reaction,¹⁹⁰ the scope and usefulness were greatly broadened. Yields of 85-90% of the purified diphenyl-



acetylenes are obtained when the aryl groups are phenyl, *o*-, *m*-, or *p*-tolyl, *o*-, *m*-, or *p*-methoxyphenyl, 3,4-dimethylphenyl, and xenyl; but with *p*-ethyl, propyl, or butyl substituents on the ring an oily impurity is formed and the yields are reduced to 50-70%. No significant variation in yield is observed with bromo or chloro compounds as starting materials or with 1,1-diaryl-2,2-dihaloethanes, although the dichloroethanes do appear to give slightly poorer results. The position of attachment of the benzene ring is not changed during the migration, and the structures of several of the tolanes were proved by synthesizing them from the corresponding stilbene dibromides with ethanolic potassium hydroxide and by reducing them to known dibenzyls. Sodium amide is as effective

¹⁸⁵ Pascal and Normand, *Bull. soc. chim. France*, [4] 13, 151 (1913).

¹⁸⁶ Curtius and Kastner, *J. prakt. Chem.*, [2] 83, 225 (1911).

¹⁸⁷ A synthesis by Jenny mentioned by Rugg and Reinert, ref. 15.

¹⁸⁸ (a) Fritsch, *Ann.*, 279, 319 (1894); (b) Battenberg, *Ann.*, 279, 324 (1894); (c) Wiechell, *Ann.*, 279, 337 (1894).

¹⁸⁹ Fritsch, *Ann.*, 329, 37 (1903).

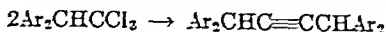
¹⁹⁰ Coleman and Maxwell, *J. Am. Chem. Soc.*, 56, 132 (1934); Coleman, Holst, and Maxwell, *ibid.*, 58, 2310 (1936).

as potassium amide in this synthesis²²⁰ and, since it is more readily prepared, would seem to be the reagent of choice. 1,1-Diphenyl-2,2-dichloroethane gives tolan in 80% yield with sodium amide.⁸¹ This method is probably the best available for the synthesis of tolan derivatives since diarylbromoethenes are easily prepared from the unsymmetrical diarylethenes which are available from diarylmethylcarbinols.

Tolan derivatives may be prepared in unspecified yield by treating unsymmetrical diaryldichloro- or diarylbromochloro-ethenes with sodium in benzene.²²¹ Under the same conditions diaryltrichloroethanes give 95% yields of the substituted stilbenes and only 2% of tolan. The action of ethanolic sodium ethoxide on unsymmetrical diphenyl- or ditolyl-dichloroethene yields mainly diarylacetic acids, but, with di-*p*-anisyl- or di-*p*-phenetyl-dichloroethenes, 80% yields of the tolan are obtained and about 20% of unchanged dihaloethene is recovered.²²²

An unusual synthesis of *o,o'*- or *p,p'*-dinitrotolan occurs when *o*- or *p*-nitrobenzal chloride is treated with ethanolic sodium ethoxide.^{82,23} With the *ortho* compound²²³ considerable heat is generated and the yields are 36–39%. The reaction is believed to go through the corresponding tolan dihalide, which has been isolated from *p*-nitrobenzal chloride.⁸² *m*-Nitrobenzal chloride²²³ gives only an acetal in this reaction. A similar reaction for the formation of *o*- or *p*-stilbenes from nitrobenzyl halides is well known and has been reported for benzyl chloride itself.²²⁴ 2-Dibromomethylanthraquinone gives a 97% yield of 2,2-dianthraquinonylacetylene dibromide merely by heating to 230–240°,²²⁵ and this loses bromine to form the acetylene in 89% yield when refluxed with diethylaniline. The same acetylene is obtained by refluxing 2-tribromomethylanthraquinone with copper bronze in nitrobenzene.²²⁶

The union of halogenated carbons to form a triple bond occurs readily in the production of 1,1,4,4-tetraphenyl-2-butyne or similar substituted compounds from 1,1-diaryl-2,2,2-trihaloethanes.²²⁷ The reaction, which is seldom clean-cut, is accomplished electrolytically in hot ethanolic hy-



drochloric acid at a lead cathode. Catalytic reduction and reduction by

⁸¹ Harris and Frankforter, *J. Am. Chem. Soc.*, **48**, 3144 (1926).

⁸² Fritsch and Feldmann, *Ann.*, **305**, 72 (1893).

⁸³ Kliegl and Haas, *Ber.*, **44**, 1209 (1911).

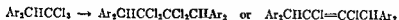
⁸⁴ Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, **34**, 139 (1902) (*Chem. Zentr.*, 1902, **1**, 1301).

⁸⁵ Ullmann and Klingenberg, *Ber.*, **46**, 712 (1913).

⁸⁶ Eckert, *Monatsh.*, **35**, 239 (1914).

⁸⁷ Brand et al., (a) *Z. Elektrochem.*, **16**, 659 (1910); (b) *Ber.*, **46**, 2935, 2942 (1913); (c) *Ber.*, **54**, 1987, 2007, 2017 (1921); (d) *Ber.*, **57**, 846 (1924); (e) *Ber.*, **72**, 1029, 1036 (1929); (f) *J. prakt. Chem.*, **115**, 335, 351 (1927); (g) *ibid.*, **127**, 219, 249 (1930).

metal combinations appear to give tetraaryl-2,2,3,3-tetrahalobutanes or 2,3-dihalo-2-butenes, and the latter usually are converted to the tetraaryl-2-butyne by reaction with zinc and acetic acid. 1,1-Di-*p*-tolyl-



2,2,2-tribromoethane is converted into tetratolyl-2-butyne in one step with zinc and acetic acid.

Somewhat similar reactions appear to occur when benzotrichloride or a substituted benzotrichloride is heated with copper powder in benzene. The yields of 1,2-diaryltetrachloroethanes are low. *o*-Chlorobenzotrichloride gives both stereoisomeric dichloroethylenes.^{208,209} Heating the *o,o'*-dichlorotolan dichlorides with zinc dust at 200° gives an 80% yield of *o,o'*-dichlorotolan. Di-(*p*-chlorophenyl)-tetrachloroethane gives the corresponding tolan when refluxed with zinc dust in acetic acid.

OTHER METHODS OF PREPARING ACETYLENES

The removal of adjacent halogens from 1,2-dihaloethylenes by metals has been used to prepare acetylenic compounds, but the method is not of great synthetic value. Dibromofumaric acid loses bromine more readily than dibromomaleic acid when treated with zinc in moist ether at 60–70° to give acetylenedicarboxylic acid in good yield.²¹⁰ A number of α,β -dichlorostyrenes, prepared from *o*-chloroacetophenones by treatment with phosphorus pentachloride, react with sodium in ether to form the sodium derivatives of the corresponding acetylenes; with water these give the acetylenes in yields reported to be "good."²¹¹



Sodium phenoxycetylide²¹² and cyclooctyne²¹³ are obtained in the same way from 1,2-dibromo-1-phenoxylethylene or tribromophenoxylethylene and 1,2-dibromocyclooctene. Zinc dust in acetone effects the removal of bromine from tolan dibromide and diphenyldiacetylene tetrabromide.²⁰⁴ The yield of diphenyldiacetylene is 85%. It is clear that whenever an acetylene dibromide is the starting material the method cannot be of synthetic value unless some source for the dibromide other

²⁰⁸ Kenner and Witham, *J. Chem. Soc.*, 97, 1960 (1910).

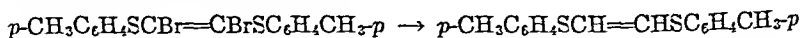
²⁰⁹ Fox, *Ber.*, 26, 653 (1893).

²¹⁰ Michael, *J. prakt. Chem.*, [2] 45, 209 (1892); [2] 52, 344 (1895).

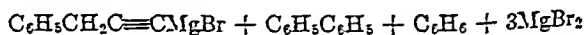
²¹¹ (a) Kuncell and Gotsch, *Ber.*, 33, 2654 (1900); (b) Kuncell and Koritsky, *Ber.*, 33, 3261 (1900); (c) Kuncell and Eras, *Ber.*, 33, 3264 (1900); 36, 915 (1903); (d) Kuncell, Eras, Müller, and Hildebrandt, *Ber. deut. pharm. Ges.*, 23, 188 (1913) (*Chem. Zentr.*, 1913, I, 1768). The constants of mentylacetylene have been corrected, ref. 43.

²¹² Dominin, *J. Gen. Chem. U.S.S.R.*, 3, 551 (1938) [*C.A.*, 33, 1282 (1939)].

han the acetylene can be found. Dibromoethylenes have been prepared from $RCH_2CBr=CH_2$ (obtained by a Grignard reagent and 2,3-dibromopropene) by adding bromine and removing hydrogen bromide with ethanolic sodium ethoxide.⁹⁰ The product is treated with zinc and ethanol to form the acetylene, but the yields are low. A similar method gave only 8% of 3-hexyne.⁶⁵ The most serious difficulty lies in the substitution which occurs during the addition of bromine to the bromoethylene. It may be possible that some olefin is formed along with the acetylene during the removal of the halogens, since *s*-dibromobis(*p*-tolylmercapto)ethylene is converted to *s*-bis(*p*-tolylmercapto)ethylene by zinc and acetic acid.²¹³



A novel method of preparing 3-phenyl-1-propyne by adding phenylmagnesium bromide to 1,2,3-tribromopropene has been described.⁹¹ The reaction is not the result of the action of unchanged magnesium but requires excess Grignard reagent, and biphenyl is produced. By adding

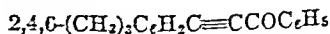
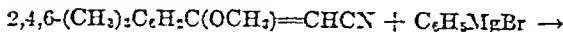


the tribromopropene to the Grignard reaction the yield is increased from 40% to 52%.⁴

Lithium phenylacetylide is produced almost quantitatively from ω -chloro- or ω -bromo-styrene by phenyllithium or butyllithium.²¹⁴ The reaction does not appear to be a simple dehydrohalogenation.^{214a}

Acetylenes have been obtained by the pyrolysis of bis-quaternary ammonium hydroxides.²¹⁵ From butane-1,2-bis-trimethylammonium hydroxide a 44% yield of ethylacetylene and a 56% yield of methylallene result, while from the 2,3-compound 42–47% of 1,3-butadiene and 53–53% of a mixture of methylallene and dimethylacetylene are obtained.

The formation of benzoylmesitylacetylene by the reaction of phenylmagnesium bromide and 2,4,6-trimethyl- β -methoxycinnamionitrile²¹⁵ may also be mentioned.



²¹³ Fromm and Siebert, *Ber.*, 55, 1014 (1922).

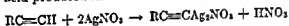
²¹⁴ (a) Wittig and Harborth, *Ber.*, 77, 315 (1944); (b) Wittig and Witt, *Ber.*, 74, 1474 (1941); (c) Gilman, Langham, and Moore, *J. Am. Chem. Soc.*, 62, 2327 (1940); (d) Gilman and Haubein, *ibid.*, 67, 1420 (1945).

²¹⁵ Hurd and Drake, *J. Am. Chem. Soc.*, 61, 1943 (1939).

²¹⁶ Fuson, Ulyot, and Hickson, *J. Am. Chem. Soc.*, 61, 410 (1939).

THE DETECTION, DETERMINATION, AND PURIFICATION OF MONOSUBSTITUTED ACETYLENES

The detection of monosubstituted acetylenes and their separation from mixtures with disubstituted acetylenes or other hydrocarbons is customarily accomplished by means of metallic derivatives. Ammoniacal silver nitrate or cuprous chloride solutions are often used to form silver or cuprous acetylides, although early investigators²¹⁷ showed that mixtures containing small amounts of monosubstituted acetylenes give no precipitate with these reagents. It requires 20% of 1-octyne with the silver reagent and 10% of 1-heptyne with the cuprous solution to give a positive acetylene test. A 5% solution of silver nitrate in 95% ethanol gives an instantaneous precipitate of a white, crystalline compound $\text{RC}\equiv\text{CAg}_2\text{NO}_3$ when treated with even traces of 1-alkynes,²¹⁷ so that they can be separated almost quantitatively from mixtures by its use.^{218,21} From 3.5 g. of 1-hexadecyne in 10 ml. of ethanol and a solution of 5.35 g. of silver nitrate in 5 ml. of water and 45 ml. of ethanol, 7.4 g. of a silver derivative results, a yield of 94.3%. The reagent has been adapted to the quantitative determination of monosubstituted acetylenes in a gas mixture.²¹⁸ A simple volumetric procedure involving the titration of the free nitric acid produced in the reaction is used.



A procedure for determining 1-heptyne by this method has been described,⁷⁴ but no data are given on the accuracy of the method. Results 2% low for 1-heptyne and 2.8% low for 1-hexyne were obtained using compounds carefully purified through their silver derivatives.²¹⁹ The procedure has been used by many workers and is the standard industrial method for the analysis of monosubstituted acetylenes. A gravimetric method is unsatisfactory because the silver complex adsorbs silver ions and decomposes above 100°, making thorough drying difficult;⁷⁴ the results are 2–3% higher than by the volumetric procedure. Acidic, basic, and sulfur impurities must be removed from the mixture in the volumetric procedure. The ethanolic silver solution should not be heated since this produces violently explosive silver fulminate.

Phenylacetylene has been determined²²⁰ by precipitation of the cuprous derivative from ethanolic solution with ammoniacal cuprous chloride.^{221,194} After vigorous shaking the precipitate is filtered and

²¹⁷ Béhal, *Ann. chim.*, [6] **15**, 408 (1888).

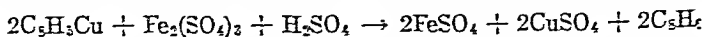
²¹⁸ Chavastelon, *Compt. rend.*, **125**, 245 (1897).

²¹⁹ Hurd and Christ, *J. Org. Chem.*, **1**, 141 (1936).

²²⁰ Hein and Meyer, *Z. anal. Chem.*, **72**, 30 (1927).

²²¹ Illosvay Nagy Illosva, *Ber.*, **32**, 2697 (1899).

washed with water, ethanol, and ether, is dried, and is either weighed or dissolved in ferric sulfate-sulfuric acid solution and titrated with permanganate. With known weights of pure phenylacetylene the results



of the two procedures are in agreement and are 0.38% and 0.90% high. No determinations on hydrocarbon mixtures of known phenylacetylene content were given. The precipitation of the cuprous derivative of 1-heptyne with aqueous ammoniacal cuprous chloride is slow, and with concentrated ammonia solutions incomplete.⁷⁴

Silver acetylides are rather soluble in concentrated silver nitrate solution because of the formation of a complex between the silver acetylide and silver ion⁷⁵ (Table IX). Dilution of the solution caused a

TABLE IX
SOLUBILITY OF ACETYLENES IN 50% AQUEOUS SILVER NITRATE

| Acetylene | Volume % |
|-------------------|----------|
| 1-Butyne | 15 |
| 1-Pentyne | 10 |
| 1-Heptyne | 6 |
| Phenylacetylene | 8 |
| Dialkylacetylides | 0 |

silver derivative to precipitate. Raman spectra studies indicate that the triple bond is involved in the complex formation, and the suggestion has been made that the complexes may be similar to those formed by olefins.⁷⁶ It is odd that dialkylacetylides do not form such coordination compounds. Very probably the somewhat erratic results observed in the determination of acetylides as their metallic derivatives arise from the variable solubility of the complexes in the solution.

A method has been published for the determination of acetylides based on their reaction with methanol in the presence of mercuric oxide-boron trifluoride catalyst, to produce ketals which are subsequently hydrolyzed to ketones.⁷⁷

In neutral or acidic solution mercuric salts give addition products of

⁷⁴ Taufen, Murray, and Cleveland, *J. Am. Chem. Soc.*, **63**, 3509 (1941).

⁷⁵ Winstein and Lucas, *J. Am. Chem. Soc.*, **60**, 826 (1938); Keller, *Chem. Ber.*, **23**, 223 (1941).

⁷⁶ Wagner, Goldstein, and Peters, *Ind. Eng. Chem., Anal. Ed.*, **19**, 163 (1947).

varying composition with monosubstituted acetylenes, but in alkaline solution mercuric derivatives analogous to cuprous or silver alkynides are formed. These mercuric acetylides are prepared easily in yields of 85-95%¹ by adding a solution of the acetylene in ethanol to excess alkaline mercuric iodide^{23a} or cyanide.²⁴ The derivatives are useful for the identification of monosubstituted acetylenes because they are easily purified and have characteristic melting points.

The purification of monosubstituted acetylenes through their cuprous, silver, or mercuric derivatives has been widely used. It is common practice to decompose the first two of these with dilute hydrochloric acid, although this reagent with the cuprous or silver derivative of 1-heptyne leads to a product containing traces of halogen.²⁵ Diacetylene has been recovered from its copper derivative by treatment with potassium cyanide,^{11a} and chloro- or bromo-acetylene is obtained similarly from its mercuric derivative.²⁴ Furfurylacetylene has been purified through its copper salt by refluxing with aqueous sodium cyanide with 90% recovery; phenylacetylene was purified similarly with an 85% recovery.³ Pure 1-hexyne is obtained with only 27% loss by refluxing the recrystallized silver nitrate complex with sodium cyanide solution.^{11b} When ammonium thiocyanate is used to decompose the complex, the yield is only 40%, but the losses are said to be largely mechanical.^{11b} The formation of an acetylenic Grignard reagent is not sufficiently complete to make this derivative of value for purification.²⁶

The synthesis of 1-alkynes using sodium amide²³ assures freedom from disubstituted acetylenes if conducted properly, and in some instances an acetylenic mixture obtained by dehydrohalogenation with potassium hydroxide has been converted to 1-alkyne by treatment with sodium amide in a similar fashion.²⁷

In general the purification of monosubstituted acetylenes through their metallic derivatives is a satisfactory process entailing moderate losses. It appears to be the best method of separating these compounds from disubstituted acetylenes. Since some of these metallic derivatives, notably those of acetylene and diacetylene, are very explosive when dry, even moderate quantities should be kept moist with the solvent at all times.

Disubstituted acetylenes are occasionally purified by removal of monosubstituted isomers as metallic derivatives. Thus 1-butyne was removed from 2-butyne by passing the gaseous mixture through 50% aqueous ethanolamine containing cuprous chloride.^{11c}

^{23a} Hofmann and Kirmreuther, *Ber.*, **41**, 314 (1908); **42**, 4232 (1909).

^{23b} Moureu, *Ann. chim.*, [8] **7**, 541 (1906) note; see Straus and Kühnel, *Ber.*, **65**, 154 (1932).

²⁴ Hurd, Meinert, and Spence, *J. Am. Chem. Soc.*, **52**, 1133 (1930).

²⁵ Levina and Potapova, *J. Gen. Chem. U.S.S.R.*, **7**, 353 (1937) [*C.A.*, **31**, 4652 (1937)].

EXPERIMENTAL PROCEDURES

Carefully tested directions for the synthesis of the following acetylenic compounds have appeared in *Organic Syntheses*.

Acetylenedicarboxylic acid from α,β -dibromosuccinic acid with methanolic potassium hydroxide.⁹

3-Cyclohexylpropyne from 3-cyclohexyl-2-bromopropene with sodium amide.²²

Phenylacetylene from ω -bromostyrene with molten potassium hydroxide.²³

Phenylpropargyl aldehyde from cinnamic aldehyde.²³

Phenylpropionic acid from ethyl cinnamate dibromide with ethanolic potassium hydroxide.¹⁰³

Tolan from stilbene dibromide.⁵

Stearolic acid from methyl oleate dibromide with potassium hydroxide in amyl alcohol.^{223c}

1-Hexyne from Sodium Acetylide and *n*-Butyl Bromide in Liquid Ammonia ²²

The apparatus consists of a 5-l. three-necked flask equipped with a mercury-sealed stirrer and an efficient Dry Ice-cooled condenser. The stirrer may be a well-balanced glass loop or a wire stirrer.²² The condenser ^{45b} consists of a several-turn vertical coil of 1:7 gradient made of block tin tubing not less than $\frac{1}{2}$ in. in internal diameter, fitting snugly inside a double-walled jacket made of a tin can inserted inside a slightly larger can and separated from it by a layer of asbestos. The top of the annular space is sealed with plaster of Paris, and the coil is soldered in at top and bottom. (To arrest corrosion the condenser is cleaned and dried after each run.) Glass condensers, although considerably less efficient, may be used in small runs. Two liquid-ammonia condensers ¹²² mounted one above the other have also been used.¹⁴²

About 2 L. of commercial anhydrous liquid ammonia is placed in the 5-l. flask, and 1.5 g. of powdered, hydrated ferric nitrate (0.3 g. for each

²² Allen and Edens, *Org. Syntheses*, 25, 92 (1945).

²³ Adkins and Burks, *Org. Syntheses*, 27, 76 (1947).

²² These directions are a condensation of those found in the Ph.D. Thesis of Greenlee, Ohio State University, 1942 (see ref. 144). The preparations of sodium amide and of sodium acetylide given in *Inorganic Syntheses*, 2, 128, 75 (1946), specify more concentrated solutions which probably work equally well in the final step.

¹²² Hershberg, *Ind. Eng. Chem., Anal. Ed.*, 8, 313 (1936); *Org. Syntheses*, 17, 31 (1937); *Coll. Vol. 2*, 117 (1943).

gram atom of sodium) is added. After vigorous stirring for several minutes, 2 g. of sodium is added; a vigorous reaction occurs, and the solution becomes black from the colloidal particles of iron. When the reaction subsides the blue color of sodium is visible around the edges of the mixture and hydrogen is slowly evolved. To improve visibility the frost on the outside of the flask may be removed with ethanol. A brisk stream of dry air is bubbled through the solution for fifteen to twenty seconds. This converts some of the sodium to sodium peroxide which activates the catalyst. The evolution of hydrogen is more rapid for a short time but soon ceases, and 114 g. of sodium (a total of 116 g. or 5 gram atoms plus 1 g.) is added in 15- to 23-g. quantities, enough time being allowed between additions for complete conversion to sodium amide (disappearance of the blue color). The stirrer is operated slowly during this procedure, and at the end it is run at high speed for a few minutes to wash down sodium spattered on the upper walls of the flask. The sodium amide can be seen around the walls of the flask as tiny colorless crystals like grains of sand; the liquid is still dark from the iron catalyst. A rapid stream of tank acetylene which has been passed through concentrated sulfuric acid and then through a tower of soda lime and anhydrous calcium chloride is introduced at a point below the stirrer, which is run at moderate speed. The reaction mixture immediately becomes milky and clears up shortly before the theoretical amount of acetylene has been added, when it turns dark again. No gases are evolved during the addition of acetylene.

The acetylene addition tube is replaced by a dropping funnel, and 617 g. (4.5 moles) of *n*-butyl bromide is added rather rapidly. The solvent refluxes somewhat more vigorously for about two hours, and the solution is stirred rapidly for a total of six and one-half hours. Water is then added at moderate rate from the dropping funnel until the flask is nearly full; some acetylene is evolved during the process. Two layers are formed, and the lower (aqueous ammonia) is siphoned off and discarded. The upper layer is shaken with water, ice-cold 1:1 hydrochloric acid (which removes finely divided iron), and dilute sodium carbonate solution, and is dried over calcium chloride. The crude product (350 g., 95% yield) is fractionated through a column having about six theoretical plates, and the fraction that boils at 70.5–71°/750 mm. (uncor.) is collected; this weighs 320 g. (87% yield). Refractionation of fore-run and residue gives an additional 10 g. of material with the same boiling point and refractive index (total yield 89%). Pure 1-hexyne has the following constants: b.p. 71.4°/760 mm., m.p. –132.09°, d_4^{20} 0.7156, n_D^{20} 1.3990.

p-Tolylacetylene ⁵⁰

(a) Preparation of 1-*p*-Tolyl-1-chloroethylene. To 189 g. (0.9 mole) of phosphorus pentachloride in a 250-ml. Claisen flask fitted with a dropping funnel and drying tube and cooled in a bath of ice and salt, 110 g. (0.82 mole) of *p*-tolyl methyl ketone is added during one hour. The reaction mixture is left in the cooling bath for an hour and at room temperature for twelve hours. Phosphorus oxychloride is removed under reduced pressure, and the residue is distilled through a small column. The product is an oil, b.p. 81–83°/10 mm., yield 85 g. (68%).

At 70° a 75% yield is obtained. The use of pure phosphorus pentachloride and rapid distillation are important.⁵¹

(b) Conversion of 1-*p*-Tolyl-1-chloroethylene to *p*-Tolylacetylene. A mixture of 85 g. (0.56 mole) of 1-*p*-tolyl-1-chloroethylene, prepared as above, and 50 g. (0.78 mole) ²¹ of potassium hydroxide in 100 ml. of absolute ethanol is refluxed for twenty-four hours. The mixture is poured into a liter of ice water, the oil separated, and the aqueous layer extracted with ether. The oil and ether are combined and dried over potassium hydroxide; the ether is removed, and the residue is distilled under reduced pressure; b.p. 79–82°/31–33 mm.; yield 31 g. (48%).

p-Bromophenylacetylene ⁴⁹

(a) Preparation of 1-(4-Bromophenyl)-1-chloroethylene and 1-(4-Bromophenyl)-1,1-dichloroethane. A mixture of 95 g. (0.48 mole) of *p*-bromoacetophenone and 107 g. (0.51 mole) of phosphorus pentachloride in a 500-ml. round-bottomed flask provided with a reflux condenser is heated to 70° in an oil bath. Rapid evolution of hydrogen chloride begins when the *p*-bromoacetophenone melts, and the reaction is over in about ten minutes. The clear yellow liquid is distilled under reduced pressure. After the phosphorus oxychloride has been removed (b.p. 45–50°/18 mm.), 19 g. (18%) of the monochloroethylene derivative, b.p. 118–122°/18 mm., and 62.5 g. (52%) of the dichloroethane, b.p. 126–127°/18 mm., are obtained. These fractions need not be separated for the next reaction.

(b) Conversion of the Chloroethylene and Dichloroethane to the Acetylene. A mixture of 82 g. (0.34 mole) of chloro compounds obtained above and 400 g. of ethanolic potassium hydroxide (25% by titration, 1.8 moles) in a 1-l. round-bottomed flask provided with a reflux condenser, is refluxed for three hours in an oil bath and poured into a liter

²¹ The potassium hydroxide contains about 13% of water and other impurities.

of ice water. The oil is separated, and the aqueous portion is extracted with ether. The oil and ether are combined and dried over potassium hydroxide or potassium carbonate. The ether is removed, and the product is distilled under reduced pressure from a Claisen flask having a wide side arm, b.p. 88–90°/16 mm. The *p*-bromophenylacetylene crystallizes in the receiver and is recrystallized from ethanol. The yield is 32.5 g. (53%) of colorless crystals, m.p. 64–65°. There is no advantage in dropwise addition of the chloro compound to the ethanolic potassium hydroxide.

1-Phenyl-1-hexyne¹⁷²

To 11.5 g. (0.5 gram atom) of sodium wire in 200 ml. of toluene in a 1-l. three-necked round-bottomed flask, equipped with a reflux condenser, mercury-sealed stirrer, and dropping funnel, is added slowly with stirring 51 g. (0.5 mole) of phenylacetylene.⁷⁹ The flask is kept at 35–40°, since above this temperature the sodium derivative forms a gelatinous mass. To the suspension of the acetylide is added with stirring during two hours 114 g. (0.5 mole) of *n*-butyl *p*-toluenesulfonate²²¹ while the temperature is maintained at 70°. After three hours at 80° the reaction mixture is cooled and treated with water; ether is added if an emulsion forms, and the ether-toluene solution is washed and dried over solid potassium hydroxide or potassium carbonate. The product is distilled under reduced pressure, and, after a small fore-run of phenylacetylene, 51–55 g. (65–70%) of 1-phenyl-1-hexyne is obtained, b.p. 109–110°/12 mm. On redistillation the compound boils at 94–95°/4 mm.; d_4^{20} 0.9024 and n_D^{20} 1.5347.

The sodium derivative of phenylacetylene may also be prepared with sodium amide. The reagent is finely powdered under mineral oil and transferred to the flask as a suspension. Anhydrous ether is then added, and the oil is removed by several washings with ether. An alternative method is to prepare the sodium amide in liquid ammonia and displace this solvent with ether.¹⁷⁷ An excess of sodium amide and of butyl *p*-toluenesulfonate results in a 57% yield of 1-phenyl-1-hexyne.¹²²

Dibutyl ether may be used instead of toluene in the preparation, or the sodium derivative may be prepared in ether with sodium and the ether replaced by a higher-boiling solvent. Mineral oil may be added for the last part of the reaction.

¹⁷² Roos, Gilman, and Beaber, *Org. Syntheses, Coll. Vol. 1*, 145, 2nd ed., 1941.

The Purification of 1-Hexyne ¹¹²⁵

To a solution of 41 g. (0.5 mole) of 1-hexyne in 160 ml. of 95% ethanol is added slowly and with stirring a solution of 170 g. (1 mole) of silver nitrate in 250 ml. of water. The white precipitate of $C_6H_9C\equiv CAg_2NO_3$ is filtered, washed with water, and recrystallized from 1.8 l. of 95% ethanol. The crystals are washed thoroughly with water and refluxed for three hours with a solution of 115 g. of sodium cyanide in 250 ml. of water. The regenerated 1-hexyne is dried over calcium chloride and distilled; b.p. 70.5–70.7° cor./747 mm., yield 30 g. (73%).

TABULAR SURVEY OF ACETYLENES SYNTHESIZED BY THE METHODS DESCRIBED IN THIS CHAPTER

Only those acetylenes are included that have been prepared by methods covered in this review and that have been reported in *Chemical Abstracts* through 1947. If other methods are of synthetic value for one of these compounds, they are included, but the references may not be complete. An attempt has been made to include mainly references dealing with synthesis, and with the more common acetylenes only recent references or those of definite synthetic value are listed. Where information is available, yields have been calculated allowing for recovered starting material. The methods of synthesis are indicated as follows.

1. Dehydrohalogenation with ethanolic potassium hydroxide or other alkaline reagents except alkali amides.
2. Dehydrohalogenation with sodium amide or potassium amide.
3. Alkylation of metallic derivatives of acetylenes in ether or other inert solvents.
4. Alkylation in liquid ammonia.
5. Other methods discussed in this review.
6. Methods not discussed in this review.

A question mark (?) indicates some uncertainty in the structure or synthesis. A star (*) indicates that the yield was of crude material.

| Formula | Compound | Method | Yield % | References * |
|--------------------------------|-------------------|--------|----------|---|
| C₂ | | | | |
| C ₂ Br ₂ | Dibromoacetylene | 1 | 15 | 233, 234 |
| | | 6 | — | 235 |
| | | 6 | 23 | 236 |
| C ₂ Cl ₂ | Dichloroacetylene | 1 | 65 | 75, 76, 77, 237 |
| | | 6 | — | 235, 238 |
| C ₂ IIBr | Bromoacetylene | 1 | Good, 45 | 224, 239, 240, 241, 99a, 242, 243, 244, 2, 56 |
| C ₂ HCl | Chloroacetylene | 1 | Good | 224, 56, 245, 246, 247 |
| | | 6 | — | 71b |
| C ₂ II | Iodoacetylene | 6 | — | 248 |
| C ₂ I ₂ | Diiodoacetylene | 1 | 25 | 249 |
| | | 6 | 80-93 | 250, 251, 252, 253, 254, 255, 256, 257, 111b |
| | | 6 | 54-63 | 258, 259 |

C₃

| | | | | |
|---|-----------------------|---|-------|--|
| C ₃ IBrO ₂ | Bromopropiolic acid | 1 | — | 71a |
| C ₃ HClO ₂ | Chloropropiolic acid | 6 | 74 | 235 |
| | | 1 | — | 71b |
| C ₃ HIO ₂ | Iodopropiolic acid | 6 | 19 | 235 |
| | | 1 | 80 | 99a |
| C ₃ I ₂ Br ₂ | 1,3-Dibromo-1-propyne | 6 | — | 260, 111b |
| | | 1 | — | 261 |
| C ₃ I ₂ O ₂ | Propiolic acid | 6 | 70-87 | 111, 262, 263, 264, 164, 165 148a |
| C ₃ I ₂ Br | 1-Bromo-1-propyne | 1 | 25 | 61 |
| | | 6 | — | 10c |
| C ₃ I ₂ Br | 3-Bromo-1-propyne | 6 | 65 | 265, 266, 267, 268 |
| C ₃ II ₄ | Propyne | 1 | 67-85 | 10, 226, 160, 11b, 65, 260, 270 |
| | | 4 | 84 | 135, 137, 139, 142, 143, 144, 185, 271, 272, 273 |

See p. 62 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

ORGANIC REACTIONS

| Formula | Compound | Method | Yield % | References * |
|-----------|-------------------|--------|---------|-----------------------------|
| C_3H_4O | 2-Propyn-1-ol | 1 | 66-69 | 57, 266, 268, 274, 275, 368 |
| | | 6 | — | 276 |
| | | 6 | 10 | 277 |
| C_3H_4O | Methoxyacetylene | 1 | — | 278 |
| C_3H_5N | 3-Amino-1-propyne | 1 | Poor | 276 |

C₄

| | | | | |
|--------------|-----------------------------|---|----------|--|
| C_4H_2 | 1,3-Butadiyne | 1 | 80-90 | 180a, 279 |
| | | 6 | Poor | 111b, 280, 281, 270 |
| $C_4H_2O_4$ | Acetylenedicarboxylic acid | 1 | 73-88 | 9, 111a, b, 68, 71c, d, 210, 262, 282, 283, 284, 285, 286, 287 |
| | | 6 | Poor, 34 | 161, 164, 214d |
| $C_4H_4O_2$ | 2-Butynoic acid | 1 | 16-87 | 126, 288, 289, 290, 291, 292, 293, 210, 294, 295, 296, 297, 298, 299 |
| | | 5 | — | 298, 299 |
| | | 6 | — | 161, 300 |
| C_4H_5BrO | 1-Bromo-3-methoxy-1-propyne | 1 | — | 261, 301 |
| $C_4H_5NO_2$ | 1-Nitro-1-butyne | 1 | — | 67 |
| C_4H_6 | 1-Butyne | 1 | 34 | 4 |
| | | 2 | 60 | 32, 33 |
| | | 4 | 65-78 | 144a, 142, 143, 136a, 302, 138, 139, 149a, c, d, 273 |
| | 2-Butyne | 1 | 65 | 80b, 78, 269, 60, 41, 11a |
| | | 4 | 81 * | 271, 303, 304, 10b, 185 |
| C_4H_6O | 3-Butyn-2-ol | 1 | — | 305, 306 |
| | | 6 | 57 | 307, 308, 309 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------|---------------------|--------|---------|---------------------|
| C_4H_6O | 3-Butyn-1-ol | 1 | — | 305, 310 |
| | | 6 | 65 | 311, 277 |
| | 3-Methoxy-1-propyne | 1 | 80 | 12, 274, 312, 313 |
| | | 2 | 61 | 26, 28 |
| $C_4H_6O_2$ | Ethoxyacetylene | 1 | 50-53 | 18c, 278, 314 |
| | | 3 | — | 316, 309 |
| | 2-Butyne-1,4-diol | 3 | — | 305, 161, 315, 317, |
| | | 6 | — | 180a |

 C_5

| | | | | |
|-------------------------|--------------------------|---|-------|---|
| $C_5H_8O_4$ C_5H_8 | 2-Pentyno-1,5-dioic acid | 1 | — | 318 |
| | | 4 | 38 | 186 |
| | | 6 | 50-73 | 310 |
| $C_5H_8O_2$ | 1-Penten-4-yne (?) | 3 | 70-75 | 164, 169, 170, 144, 152 |
| | | 6 | 45-49 | 70b, 320, 288, 46, 78, 321, 322 |
| | 3-Pentynoic acid | 1 | 10-15 | 70b |
| | | 1 | 40 | 70b, 323, 111c |
| C_5H_7Cl | 4-Pentynoic acid | 4 | 57 | 144 |
| $C_5H_7NO_2$ | 5-Chloro-1-pentyne | 1 | — | 67 |
| C_5H_8 | 1-Nitro-1-pentyne (?) | 1 | 55 | 24c, 78, 84, 00, 324 |
| | | 2 | 30-62 | 23 |
| | | 4 | 00 | 144, 142, 143, 136a, 304, 80, 139 |
| | | 1 | 35 | 325, 78, 324, 320, 327 |
| | 2-Pentyne | 3 | 40 | 32, 41 |
| | | 4 | 59 | 144 |
| | | 1 | 18-60 | 125, 327, 328, 78, 329, 330, 35, 36 |
| | 3-Methyl-1-butyne | 2 | 25-31 | 31, 85, 36 |
| | | 4 | 29-50 | 139 |
| | | 1 | — | 305 |
| C_5H_8O | 1-Pentyn-3-ol | 6 | 50 | 331, 309 |
| | | 1 | Poor | 332 |
| | 4-Pentyn-1-ol | 1 | 75 | 314 |
| | n-Propoxyacetylene | 1 | — | 333, 331, 335, 312 |
| | 3-Methoxy-1-propyne | 1 | 88 * | |

See p. 82 for explanation of symbols and methods in this table.
 * References 231-319 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|----------------|----------------------------------|--------|---------|--------------|
| C_5H_8O | 3-Ethoxy-1-propyne (?) | 2 | 81 | 26, 28 |
| | 1-Methoxy-2-butyne | 3 | 15 | 28 |
| | | 6 | 61 | 102, 336 |
| | 4-Methoxy-1-butyne | 1 | — | 305, 337 |
| | | 4 | 60-75 | 151 |
| $C_5H_8O_2$ | Propynal dimethylacetal | 1 | — | 338 |
| $C_5H_{10}BrN$ | Ethynyltrimethylammonium bromide | 1 | — | 339, 340 |

C₆

| | | | | |
|-------------|------------------------------|---|--------------|---|
| C_6H_7BrO | 5-Bromo-2-ethynylfuran | 1 | — | 341 |
| | | 5 | 32 | 16d |
| C_6H_4O | 2-Furylacetylene | 1 | 25 | 8, 342 |
| C_6H_6 | 1,5-Hexadien-3-yne | 6 | — | 343, 344 |
| | 1,4-Hexadiyne | 1 | — | 344 |
| | 1,5-Hexadiyne | 1 | — | 344, 274, 345, 346, 347, 348, 349, 350, 305, 78, 316 |
| | 2,4-Hexadiyne | 1 | — | 316, 78 |
| | | 6 | 42 | 271, 344 |
| $C_6H_6O_4$ | Propargylmalonic acid | 1 | — | 111c |
| C_6H_7Br | 1-(or 2)-Bromo-1-hexen-5-yne | 1 | — | 305, 344, 346 |
| C_6H_8 | 1-Hexen-3-yne | 3 | Satisfactory | 184 |
| | | 4 | 24-31 | 186 |
| | 1-Hexen-5-yne | 1 | — | 351 |
| C_6H_5O | 1-Hexyn-5-one | 1 | Poor | 323 |
| $C_6H_5O_2$ | 2-Methyl-4-pentynoic acid | 1 | — | 323, 111c |
| C_6H_7BrO | 2-Bromoethyl 3-butyryl ether | 4 | — | 151 |
| C_6H_{10} | 1-Hexyne | 1 | 75 | 24c, 352, 78 |
| | | 2 | 60 | 28, 48a, |
| | | 3 | 72 | 164, 165 |
| | | 4 | 90 | 144, 142, 143, 135, 219, 86, 149a, 54, 139, 140, 112b |
| | 2-Hexyne | 1 | — | 78, 352, 353 |
| | | 3 | — | 28, 41 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

SYNTHESIS OF ACETYLENES

| Formula | Compound | Method | Yield % | References * |
|----------------|-------------------------------|--------|---------|---------------------|
| $C_6H_{10}O$ | 2-Hexyne (Continued) | 4 | — | 140 |
| | 3-Hexyne | 1 | Poor | 66, 133 |
| | | 3 | 20 | 165 |
| | | 4 | 75 | 144, 187, 140 |
| | | 5 | 8 | 66 |
| | 4-Methyl-1-pentyne | 1 | 50 | 354 |
| | | 5 | — | 90 |
| | 4-Methyl-2-pentyne | 1 | — | 79c |
| | | 3 | 36 | 34, 36 |
| | 3,3-Dimethyl-1-butyne | 1 | 27-73 | 117, 6, 116, 78, 10 |
| | | | | 355, 356 |
| | 3-Hexyn-1-ol | 1 | 71 | 357, 358 |
| | | 6 | 28 | 33, 357 |
| | n-Butoxyacetylene | 1 | 34-56 | 18c, 314 |
| | 4-Ethoxy-1-butyne | 4 | 60-75 | 151 |
| $C_6H_{10}O_2$ | 5-Methoxy-1-pentyne | 4 | 70 | 332 |
| | 2-Butynal dimethyl acetal | 1 | 70-80 | 359, 360 |
| | 1,4-Dimethoxy-2-butyne | 3 | 63 | 101, 305 |
| C_7 | | | | |
| $C_7H_5BrO_2$ | 5-Bromo-2-furylpropionic acid | 1 | 69 * | 16d |
| C_7H_5N | 3-Pyridylacetylene | 1 | 42 | 70c |
| C_7H_8 | 1,6-Heptadien-3-yne | 3 | Good | 170 |
| | 1,6-Heptadiyne | 4 | 40-43 | 144, 155 |
| $C_7H_8O_4$ | Methylpropargylmalonic acid | 1 | — | 111c |
| C_7H_{10} | 5-Methyl-3-hexen-1-yne | 1 | 33 | 361 |
| | Cyclopentylacetylene | 2 | 9 | 41 |
| | Cycloheptyne (7) | 1 | — | 362, 363 |
| $C_7H_{10}O$ | 2-Ethoxy-1-penten-4-yne | 1 | — | 364 |
| | (7) | | | |
| C_7H_{12} | 1-Heptyne | 1 | 0-88 * | 24a, b, 37, 65, 74 |
| | | | | 80a, 328, 329 |
| | | | | 352, 365, 366 |
| | | | | 191c, 367, 369 |
| | | | | 370 |
| | | 2 | 60 | 28, 4, 27, 37, 48c |
| | | 4 | 83 | 144, 142, 143, |
| | | | | 136c, 219, 54, |
| | | | | 149a, b, 139, |
| | | | | 140 |
| | | 5 | Good | 110, 225 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|----------------|-------------------------|--------|--------------|------------------|
| C_7H_{12} | 2-Heptyne | 1 | — | 217, 296, 371 |
| | | 3 | Satisfactory | 184, 41 |
| | | 4 | 38 | 142, 143 |
| | 3-Heptyne | 1 | — | 217, 372 |
| | | 2 | 40 | 28 |
| | 5-Methyl-1-hexyne | 1 | 42 | 373, 84 |
| | | 4 | 68-70 | 144, 136 |
| | 5-Methyl-2-hexyne | 1 | — | 79 <i>d</i> |
| | 2-Methyl-3-hexyne | 3 | 39 | 35, 36 |
| | 4,4-Dimethyl-1-pentyne | 1 | — | 82 |
| | 4,4-Dimethyl-2-pentyne | 2 | 37 | 38 |
| | | 1 | — | 82, 374 |
| | | 3 | 55 | 117 <i>a</i> |
| $C_7H_{12}O_2$ | Propynal diethyl acetal | 1 | 35 | 7, 100, 338, 375 |

 C_8

| | | | | |
|--------------|-----------------------------|---|--------------|---|
| $C_8H_4Cl_2$ | 2,6-Dichlorophenylacetylene | 1 | — | 376 |
| C_8H_5Br | Bromoethynylbenzene | 1 | Satisfactory | 99 <i>a</i> , 377 |
| | | 6 | 88 | 235, 378, 379, 380 |
| C_8H_5Cl | 4-Bromophenylacetylene | 1 | 53 | 49, 43, 381 |
| | Chloroethynylbenzene | 1 | — | 99 <i>a</i> |
| | | 6 | 67, 70 | 183, 382 |
| C_8H_5I | 2-Chlorophenylacetylene | 5 | 66 | 16 <i>a</i> |
| | 4-Chlorophenylacetylene | 1 | 75 | 43, 381 |
| | Iodoethynylbenzene | 5 | — | 383, 73 <i>b</i> |
| | | 6 | 92 | 384, 385, 183, 99 <i>a</i> , 377, 386, 251, 387 |
| $C_8H_5NO_2$ | 2-Nitrophenylacetylene | 5 | Good | 104 <i>i</i> , 388, 16 <i>e</i> |
| | 3-Nitrophenylacetylene | 1 | — | 389 |
| | | 5 | — | 390, 104 <i>d</i> |
| | 4-Nitrophenylacetylene | 5 | Quant. | 391, 104 <i>h</i> , 392, 381 |
| C_8H_6 | Phenylacetylene | 1 | 67 | 20, 23, 105, 45, 99 <i>a</i> , 377, 393, 394 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|----------------|--------------------------------------|--------|------------|--------------------------|
| | Phenylacetylene (<i>Continued</i>) | 2 | 83 | 183, 28, 26, 65, 48a, 54 |
| $C_8H_5ClO_3P$ | 2-Chlorophenylethynylphosphonic acid | 5 1 | 82 68 * | 214, 72e 16a |
| C_8H_5O | Phenoxyacetylene | 1 | 60-80 | 18 |
| | 2-Hydroxyphenylacetylene | 6 | 55 | 394a |
| $C_8H_7O_3P$ | Phenylethynylphosphonic acid | 1 | — | 16a |
| $C_8H_5O_2$ | 1,6-Heptadiyno-4-carboxylic acid | 1 | — | 323, 395 |
| C_8H_{10} | 3-Ethynyl-1,5-hexadiene (?) | 3 | — | 164 |
| | 3-Ethynyl-1,5-hexadiene | 4 | 85-93 * | 144, 152 |
| | 1,7-Octadiyne | 1 | — | 396 |
| | 1-Ethynyl-1-cyclohexene | 2 | — | 397, 398 |
| $C_8H_{10}O$ | bis(3-Butynyl) ether | 4 | 60-75 | 151 |
| $C_8H_{10}O_2$ | 2,6-Octadiyne-1,8-diol | 5 | — | 316, 399, 400 |
| $C_8H_{10}O_4$ | Ethyl acetylenedicarboxylate | 1 | 13 | 401, 283 |
| | | 5 | Poor | 210 |
| | | 6 | Good | 402, 111b |
| $C_8H_{11}Cl$ | Chloroethynylcyclohexane | 6 | 48 | 382 |
| C_8H_{12} | 1-Octen-3-yne | 4 | — | 186 |
| | 1-Octen-4-yne | 3 | 32 | 144 (170) |
| | 6-Methyl-3-hepten-1-yne | 1 | — | 361 |
| | 1-Cyclopentylpropyne | 3 | 50 | 41 |
| | 3-Cyclopentylpropyne | 2 | 65 | 41 |
| | Cyclohexylacetylene | 1 | 46 | 125, 403, 404, 227 |
| | | 2 | 6 † | 41 |
| | Cyclooctyne | 5 | 32 | 212 |
| C_8H_{14} | 1-Octyne | 1 | — | 80a, 296, 329, 405 |
| | | 2 | 75 | 28, 86, 48a |
| | | 4 | 72 | 144, 142, 143, 406, 140 |
| | 2-Octyne | 1 | — | 83, 217, 296, 366 |
| | | 3 | 81 | 28, 41 |
| | | 4 | 84 | 144, 142, 143, 140 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

† This is the overall yield from cyclohexanol and is not to be compared with the 46% yield of method 1 which is for the last step only.

| Formula | Compound | Method | Yield % | References * |
|----------------|-------------------------------|--------|---------|----------------------------------|
| C_8H_{14} | 3-Octyne | 2 | 23 | 28 |
| | | 3 | 70 | 184 |
| | | 4 | 67 | 144, 187, 142, 143, 192, 140 |
| | 4-Octyne | 4 | 60-81 | 144, 187, 54, 142, 143, 406, 140 |
| | | 5 | 58 | 180a |
| $C_8H_{14}O$ | 3-Ethyl-3-methyl-1-pentyne | 2 | 45 | 39 |
| | Butyl 3-butyne ether | 4 | 60-75 | 151 |
| | Isoamyl propargyl ether | 1 | — | 333 |
| | 1-Methoxy-2-heptyne | 3 | 42 | 177 |
| $C_8H_{14}O_2$ | 3-Butynyl-2-ethoxyethyl ether | 4 | 60-75 | 151 |
| | 1,4-Diethoxy-2-butyne | 3 | 45 | 101 |
| | 2,5-Dimethoxy-3-hexyne | 3 | 21 | 101 |
| | 2-Butynal diethyl acetal | 1 | — | 359, 360 |

 C_9

| | | | | |
|-----------------|-----------------------------------|---|-------|-----------------------------------|
| $C_9H_4Cl_2O_2$ | 2,6-Dichlorophenyl-propionic acid | 1 | — | 376 |
| $C_9H_4N_2O_6$ | 2,4-Dinitrophenyl-propionic acid | 1 | 24 | 407 |
| $C_9H_5BrO_2$ | 4-Bromophenylpropionic acid | 1 | 80 | 408, 409 |
| $C_9H_5ClO_2$ | 2-Chlorophenylpropionic acid | 1 | 68 | 16a |
| C_9H_5N | 2-Ethynylbenzonitrile | 5 | 25 | 16b |
| $C_9H_5NO_4$ | 2-Nitrophenylpropionic acid | 1 | 79 | 407, 104h, i, 410, 16c |
| | 3-Nitrophenylpropionic acid | 1 | — | 390, 389, 104d |
| | 4-Nitrophenylpropionic acid | 1 | — | 96b, 391, 104h |
| | | 6 | | 411 |
| $C_9H_6N_2O_4$ | 1-(2,4-Dinitrophenyl)-1-propyne | 1 | — | 121 |
| C_9H_6O | Phenylpropynal | 6 | 70-81 | 228, 100, 338, 412, 413, 414, 415 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|--------------------------|---|------------------------|---------|--|
| $C_9H_8O_2$ | 3,4-Methylenedioxy-phenylacetylene | 1 | 60 | 377, 416 |
| | Phenylpropionic acid | 1 | 76-80 | 103, 417, 383, 418, 104j, 419, 420, 294, 421 |
| | | 6 | Good | 104j, 422, 99a, 423, 214c |
| C_9H_7BrO | 2- (or 3-) Bromo-4-methoxyphenylacetylene | 5 | — | 424 |
| | 4-Bromophenyl propargyl ether | 1 | 50 | 423 |
| C_9H_7Cl | 1-Chloroethynyl-4-methylbenzene | 1 | — | 211a |
| | | 6 | 52 | 382 |
| C_9H_7ClO | 1-Chloroethynyl-4-methoxybenzene | 1 | — | 211c |
| | | 6 | 52 | 382 |
| $C_9H_7NO_2$ | 1-(4-Nitrophenyl)-1-propyne | 1 | — | 121 |
| $C_9H_7NO_2$ | 2-Nitro-5-methoxyphenylacetylene | 5 | 48 | 16e |
| C_9H_8 | <i>p</i> -Tolylacetylene | 1 | 48-57 | 50, 51, 4 |
| | | 2 | 64 | 49a, 42, 72e |
| | | 5 | — | 211a, d, 381, 104e |
| | 1-Phenyl-1-propyne | 1 | 70 * | 105, 426, 427, 428, 90, 429, 91 |
| | | 3 | 50-77 | 183, 41, 54, 16a, 171 |
| | | 5 | 35 | 214a |
| | 3-Phenyl-1-propyne | 2 | 75 | 28, 131d, 26 |
| | | 3 | 70 | 164, 165 |
| | | 5 | 52 | 4, 90, 429 |
| | C_9H_8O | Phenyl propargyl ether | 1 | 53 |
| 2-Methoxyphenylacetylene | | 2 | Poor | 431a |
| | | 5 | 67 | 16a |
| 4-Methoxyphenylacetylene | | 5 | 62 | 16a, 104c, g, 211, 377 |
| C_9H_8N | Phenylpropargylamine | 1 | 45 | 432 |
| | | 2 | — | 433 |
| C_9H_{12} | 1,8-Nonadiyne | 4 | 84 | 144, 155 |
| | 2,7-Nonadiyne | 4 | 76 | 144 |
| | 1-Ethynyl-5-methylcyclohexene | 2 | | |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-74.

| Formula | Compound | Method | Yield % | References * |
|----------------|-------------------------------|--------|---------|-------------------|
| C_9H_{12} | 1-Propynyl-1-cyclohexene | 3 | — | 397, 398 |
| C_9H_{14} | 1-Nonen-4-yne | 3 | 88 | 170 |
| | 1-Cyclopentyl-2-butyne | 3 | 65 | 41 |
| | 1-Ethynyl-3-methylcyclohexane | 2 | — | 397, 398 |
| | 1-Cyclohexyl-1-propyne | 3 | 24 | 41 |
| | 3-Cyclohexyl-1-propyne | 1 | 66 | 434, 90, 69 |
| | | 2 | 66-87 | 29, 28, 41 |
| $C_9H_{14}O_2$ | Butylpropargyl acetate | 3 | 16 | 177 |
| C_9H_{16} | 1-Nonyne | 1 | — | 435 |
| | | 2 | 84 | 28, 27, 183 |
| | | 4 | 46 | 86, 142, 143 |
| | 2-Nonyne | 3 | 80 | 28, 183, 41, 184 |
| | 3-Nonyne | 3 | 60 | 183, 184 |
| | | 4 | 54 | 142, 143, 48a, 54 |
| | 4-Nonyne | 4 | 45 | 142, 143 |
| | 7-Methyl-3-octyne | 4 | 35 | 54 |
| | 2,6-Dimethyl-3-heptyne | 1 | 38 | 79d |
| $C_9H_{16}O$ | 1-Ethoxy-2-heptyne | 3 | 27-35 | 177, 436 |

 C_{19}

| | | | | |
|------------------|---|---|---------|----------------------|
| $C_{10}H_5NO_6$ | 2-Nitro-4,5-methylenedioxyphenylpropionic acid | 1 | 76 * | 16c |
| $C_{10}H_7NO_5$ | 3-Nitro-4-methoxyphenylpropionic acid | 1 | — | 437 |
| | 2-Nitro-5-methoxyphenylpropionic acid | 1 | 70-78 * | 16c |
| $C_{10}H_8Br_2O$ | <i>z,z</i> -Dibromo-2-methoxy-1-(1-propynyl)benzene | 1 | — | 438 |
| $C_{12}H_5O_2$ | 3,4-Methylenedioxy-1-(1-propynyl)benzene | 1 | — | 439 |
| | <i>m</i> -Tolylpropionic acid | 1 | — | 104h |
| | <i>p</i> -Tolylpropionic acid | 1 | — | 104c |
| $C_{12}H_8O_3$ | 2-Methoxyphenylpropionic acid | 1 | 51 | 16a, 440, 440a |
| | 3-Methoxyphenylpropionic acid | 1 | 96 | 441 |
| | 4-Methoxyphenylpropionic acid | 1 | — | 16a, 104g, 104c, 442 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------------|---|--------|---------|--------------------|
| $C_{10}H_8BrO$ | <i>o</i> -Bromo-2-methoxy-1-(1-propynyl)benzene | 1 | — | 438 |
| $C_{10}H_8Cl$ | 1-Phenyl-4-chloro-1-butyne | 3 | 46 | 172 |
| | 1-Chloroethynyl-4-ethylbenzene | 1 | — | 211b |
| | 1-Chloroethynyl-2,5-dimethylbenzene | 1 | — | 211a |
| $C_{10}H_8ClO$ | 1-Chloroethynyl-2-methoxy-5-methylbenzene | 1 | — | 211d |
| $C_{10}H_8N_2$ | 1-Phenyl-4-triazo-1-butyne † | 3 | — | 443 |
| $C_{10}H_{10}$ | 1-Phenyl-1-butyne | 1 | 70 | 105 |
| | | 3 | 77 | 172, 183, 73, 44 |
| | 4-Phenyl-1-butyne | 1 | — | 373 |
| | | 2 | 63 | 4, 20, 52, 44, 441 |
| | 3-(2-Methylphenyl)-1-propyne | 2 | 75 | 52 |
| | 3-(4-Methylphenyl)-1-propyne | 2 | 75 | 52 |
| | 4-Ethylphenylacetylene | 5 | — | 211b, d |
| | 2,4-Dimethylphenylacetylene | 2 | 75 | 43, 445, 86 |
| $C_{10}H_{10}O$ | 2-Ethoxyphenylacetylene | 1 | — | 446 |
| | 1-(4-Methoxyphenyl)-1-propyne | 1 | 75 | 127, 447 |
| | 2-Methoxy-5-methylphenylacetylene | 5 | — | 211d |
| | 3-Methoxy-1-phenyl-1-propyne | 3 | — | 336 |
| | 2-Hydroxy-4-phenyl-3-butyne | 1 | — | 89 |
| | | 6 | 70 | 443, 449, 415 |
| $C_{10}H_{10}O_2$ | 3,4-Dimethoxyphenylacetylene | 5 | 41 | 104b |
| $C_{10}H_{11}N$ | Methylphenylpropargylamine | 1 | 50 | 450, 265 |
| $C_{10}H_{14}$ | 1,9-Decadiyne | 4 | 41 | 451 |
| | 1-Propynyl-5-methylcycloheptene | 3 | — | 397, 398 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

† The product is unstable and loses nitrogen. It was isolated as a dibromide.

| Formula | Compound | Method | Yield % | References * |
|-----------------------|------------------------------------|--------|---------|-----------------------------|
| $C_{10}H_{14}O_2$ | 1,8-Dimethoxy-2,6-octadiyne | 3 | — | 305, 316 |
| $C_{10}H_{16}$ | 1-Decen-4-yne | 3 | Good | 170 |
| | 1-Cyclohexyl-2-butyne | 3 | 78 | 28, 41 |
| | 4-Cyclohexyl-1-butyne | 2 | 80 | 28, 30 |
| | 1-(3-Methylcyclohexyl)-1-propyne | 3 | — | 397, 398 |
| | 3-(3-Methylcyclohexyl)-1-propyne | 2 | — | 397, 398 |
| $C_{10}H_{16}Cl_2O_2$ | 1,6-Dichloro-2,5-diethoxy-3-hexyne | 3 | — | 452 |
| $C_{10}H_{16}O_2$ | Butylpropargyl propionate | 3 | 21 | 177 |
| | Amylpropargyl acetate | 3 | 10 | 177 |
| $C_{10}H_{18}$ | 1-Decyne | 1 | — | 435 |
| | | 2 | 68 | 4, 29, 86, 48a |
| | | 4 | 53 | 142, 143, 188, 136c |
| | 3-Decyne | 3 | 47 | 183 |
| | 4-Decyne | 3 | Good | 179, 183 |
| | | 4 | 42 | 142, 143 |
| | 5-Decyne | 3 | 30 | 164, 168 |
| | | 4 | 69 | 187, 142, 143, 54, 192, 140 |
| | 8-Methyl-4-nonyne | 4 | 35 | 54 |
| | 2,2,5,5-Tetramethyl-3-hexyne | 6 | 55 | 356 |
| $C_{10}H_{16}O$ | Butylpropargyl propyl ether | 3 | 34 | 177, 436 |
| $C_{10}H_{18}O_2$ | 1,4-Di- <i>n</i> -propoxy-2-butyne | 3 | 16 | 101 |
| | 2,5-Diethoxy-3-hexyne | 3 | 14 | 101 |

 C_{11}

| | | | | |
|-------------------|-----------------------------------|---|----|----------|
| $C_{11}H_7N$ | 2-Quinolylacetylene (?) | 1 | — | 70b, c |
| $C_{11}H_{10}$ | 5-Phenyl-1-penten-4-yne | 3 | 70 | 176, 170 |
| $C_{11}H_{10}O_3$ | 2-Ethoxyphenylpropionic acid | 1 | 50 | 453, 446 |
| $C_{11}H_{10}O_4$ | 2,3-Dimethoxyphenylpropionic acid | 1 | — | 454 |
| | 3,4-Dimethoxyphenylpropionic acid | 1 | — | 104b |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|---------------------|---|--------|---------|------------------|
| $C_{11}H_{11}Br$ | 3-Bromo-2,4,6-trimethylphenylacetylene | 1 | 57 | 58 |
| $C_{11}H_{11}Cl$ | 1-Chloroethynyl-2,4,6-trimethylbenzene | 1 | — | 211b |
| | 1-Chloroethynyl-4-isopropylbenzene | 1 | — | 211b |
| | 5-Chloro-1-phenyl-1-pentyne | 3 | 75 | 172 |
| $C_{11}H_{11}ClO$ | 3-Chloro-6-methoxy-2,4-dimethylphenylacetylene | 1 | 60 | 59 |
| $C_{11}H_{11}ClO_2$ | 3-Chloro-6-methoxy-2,4-dimethylphenylpropionic acid | 6 | 55 | 59 |
| $C_{11}H_{12}$ | 2,4,6-Trimethylphenylacetylene | 2 | 71 | 43, 80, 58, 191d |
| | 2,4,6-Trimethylphenylacetylene (?) | 5 | — | 211b, 43 |
| | 4-Isopropylphenylacetylene | 5 | — | 211b |
| | 3-(2,4-Dimethylphenyl)-1-propyne | 2 | 75 | 52 |
| | 3-(2,5-Dimethylphenyl)-1-propyne | 2 | 75 | 52 |
| | 1-Phenyl-1-pentyne | 1 | 70 * | 105 |
| | | 3 | 65 | 183 |
| $C_{11}H_{12}O$ | 1-Phenyl-1-pentyn-3-ol | 1 | — | 89 |
| | | 6 | — | 415 |
| $C_{11}H_{13}N$ | Ethylphenylpropargylamine | 1 | 30 | 265 |
| | Benzylmethylpropargylamine | 1 | — | 450 |
| | 4-Ethynyl-4-vinyl-1,6-heptadiene (?) | 4 | Poor | 152 |
| $C_{11}H_{14}O_2$ | 2,10-Undecadiyn-1-oic acid | 6 | 21 | 451 |
| $C_{11}H_{14}$ | 1,10-Undecadiyne | 1 | Good | 455 |
| $C_{11}H_{14}$ | 1-Undecen-3-yne | 4 | 80 | 186 |
| | 5-Cyclohexyl-1-pentyne | 2 | 88 | 28 |
| | 5-Cyclohexyl-2-pentyne | 3 | 85 | 28 |
| | 1-(3-Methylcyclohexyl)-1-butyne | 3 | — | 397, 398 |

See p. 57 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------------|---------------------------------|--------|---------|--------------------|
| $C_{11}H_{18}$ | 1-(3-Methylcyclohexyl)-2-butyne | 3 | — | 397, 398 |
| | 4-(3-Methylcyclohexyl)-1-butyne | 5 | — | 397, 398 |
| $C_{11}H_{18}O_2$ | 9-Undecynoic acid | 1 | Quant. | 456, 81, 457 |
| | 10-Undecynoic acid | 1 | 49-77 | 458, 81, 451 |
| $C_{11}H_{20}$ | 1-Undecyne | 1 | Poor | 328, 459, 460, 435 |
| | | 2 | 50-80 | 27 |
| | | 4 | 51 | 142, 143, 86 |
| | 2-Undecyne | 1 | — | 460, 461, 462 |
| | 5-Undecyne | 3 | 70 | 183 |
| | | 4 | 60 | 54 |
| | 3,3-Dimethyl-4-nonyne | 3 | 3 | 174 |
| | | 6 | 73 | 174 |

 C_{12}

| | | | | |
|---------------------|---|---|-------|----------|
| $C_{12}H_6O_4$ | Benzene-1,3-dipropynoic acid | 1 | 50-55 | 463 |
| $C_{12}H_7BrO_4$ | Benzene-1-bromoacrylic-3-propiolic acid | 1 | — | 463 |
| $C_{12}H_8$ | α -Naphthylacetylene | 1 | — | 464 |
| | β -Naphthylacetylene | 1 | 35 | 51, 465 |
| $C_{12}H_{11}BrO_2$ | 3-Bromo-2,4,6-trimethylphenylpropionic acid | 1 | 75 | 58 |
| $C_{12}H_{12}$ | 4-Phenyl-1-hexen-5-yne | 5 | 34 | 466 |
| $C_{12}H_{12}BrO$ | 1-Phenyl-3-ethoxy-4-bromo-1-butyne | 3 | 60 | 466a |
| $C_{12}H_{13}Cl$ | 1-Chloroethynyl-5-isopropyl-2-methylbenzene | 1 | — | 211b |
| $C_{12}H_{14}$ | 2,3,4,6-Tetramethylphenylacetylene | 1 | 65 | 58 |
| | 2-Methyl-5-isopropylphenylacetylene | 5 | — | 211b, d |
| | 3-(4-Isopropylphenyl)-1-propyne | 2 | 75 | 52 |
| | 1-Phenyl-1-hexyne | 1 | 70 | 105 |
| $C_{12}H_{14}O$ | | 3 | 65-70 | 172, 183 |
| | Phenylpropargyl propyl ether | 3 | — | 336 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------------|----------------------------------|--------|---------|---------------|
| $C_{12}H_{14}O$ | 1-Phenyl-3-ethoxy-1-butyne | 3 | 50 | 466a |
| $C_{12}H_{14}O_4$ | 2,10-Dodecadiyne-1,12-dioic acid | 6 | 18 | 451 |
| $C_{12}H_{18}O_4$ | 2-Dodecyne-1,12-dioic acid | 6 | 61 | 451 |
| $C_{12}H_{18}$ | 6-Cyclohexyl-1-hexyne | 2 | 87 | 28 |
| | 6-Cyclohexyl-2-hexyne | 3 | 80 | 28 |
| $C_{12}H_{22}$ | 1-Dodecyne | 1 | 24 | 467, 17 |
| | | 2 | 34 | 86 |
| | | 4 | 57 | 188 |
| | 2-Dodecyne | 1 | — | 17, 468 |
| | 3-Dodecyne | 3 | 63 | 172 |
| | 6-Dodecyne | 3 | 23 | 183 |
| | | 4 | 58 | 142, 143, 187 |
| | 2,9-Dimethyl-5-decyne | 3 | Poor | 168 |
| $C_{12}H_{22}O_2$ | 1,4-Diisobutoxy-2-butyne | 3 | 18 | 101 |

 C_{13}

| | | | | |
|-------------------|--|---|-------|---------------|
| $C_{13}H_{16}O_2$ | α -Naphthylpropionic acid | 1 | 83 | 469, 470 |
| | | 6 | — | 465 |
| $C_{13}H_{18}$ | 2-Ethynyl-3-methylnaphthalene | 1 | 45 | 124 |
| | 3-(1-Naphthyl)-1-propyne | 2 | 50 | 131c |
| $C_{13}H_{18}O$ | 3-(2-Furyl-1-phenyl)-1-propyne | 3 | 35 | 175 |
| $C_{13}H_{18}$ | 3-(5-Isopropyl-2-methylphenyl)-1-propyne | 2 | 75 | 52 |
| | 1-Phenyl-1-heptyne | 1 | 70 | 105 |
| $C_{13}H_{18}O_2$ | Phenylpropynal diethyl acetal | 1 | 80-86 | 228, 338, 412 |
| | | 6 | 68 | 414 |
| $C_{13}H_{20}$ | 5,8-Tridecadiyne | 3 | 13 | 177 |
| | 3-(trans-2-Decalyl)-propyne | 2 | 86 | 31 |
| | 3-(cis-2-Decalyl)propyne | 2 | 77 | 31 |
| $C_{13}H_{23}Cl$ | 1-Chloro-4-tridecyne | 3 | 65 | 172 |

 C_{14}

| | | | | |
|-----------------|-------------------------------|---|----|-----|
| $C_{14}H_8Br_2$ | 4,4'-Dibromodiphenylacetylene | 1 | 74 | 483 |
|-----------------|-------------------------------|---|----|-----|

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------------|----------------------------|--------|---------|--------------|
| $C_{14}H_{22}$ | 1-Tetradecyne | 1 | — | 17 |
| | 2-Tetradecyne | 1 | — | 17, 468 |
| | 7-Tetradecyne | 4 | 38 | 188 |
| $C_{14}H_{26}O_2$ | 1,4-Diisomeryloxy-2-butyne | 3 | 14 | 101 |

 C_{15}

| | | | | |
|-------------------|---|---|-------|-----------------------------|
| $C_{15}H_{13}BrO$ | 4-Bromobenzoylphenyl-acetylene | 1 | 40 | 485 |
| $C_{15}H_{13}ClO$ | 2-Chlorophenylbenzoyl-acetylene | 1 | 90 | 485 |
| $C_{15}H_{13}O$ | Benzoylphenylacetylene | 1 | 30 | 485 |
| | | 6 | 78 | 235, 99a, 373, 393, 483a, b |
| $C_{15}H_{13}O_2$ | 4-Biphenylpropionic acid | 1 | — | 486, 487 |
| $C_{15}H_{11}Br$ | 1-(4-Bromophenyl)-3-phenyl-1-propyne | 3 | 26 | 93 |
| | 3-(4-Bromophenyl)-1-phenyl-1-propyne | 3 | 50 | 93 |
| | 1,3-Diphenylpropyne | 3 | 70 | 93, 493 |
| $C_{15}H_{15}O$ | 4-Methoxydiphenyl-acetylene | 1 | — | 489 |
| | | 3 | Good | 393 |
| $C_{15}H_{21}$ | 1-(2-Cyclohexen-1-yl)-3-cyclohexylpropyne | 3 | 15 | 179 |
| $C_{15}H_{24}$ | 6,9-Pentadecadiyne | 1 | — | 490 |
| $C_{15}H_{26}$ | Cyclopentadecyne | 2 | Poor | 53 |
| $C_{15}H_{28}$ | 1-Pentadecyne | 1 | 24-25 | 79a |
| $C_{15}H_{28}O_2$ | 10-Undecyn-1-ol diethyl acetal | 1 | — | 104f |

 C_{16}

| | | | | |
|-------------------|----------------------------------|---|----|-----------|
| $C_{16}H_{12}$ | 1,4-Diphenyl-1-buten-3-yne | 5 | — | 104f |
| $C_{16}H_{12}O_2$ | p-Methoxyphenylbenzoyl-acetylene | 1 | 30 | 485 |
| | | 6 | 33 | 377, 490a |

See p. 52 for explanation of symbols and methods in this table.

* References 233-319 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-----------------------|---|--------|---------|----------------|
| $C_{16}H_{12}O_2$ | <i>p</i> -Methoxybenzoylphenyl-acetylene | 1 | 50 | 485 |
| $C_{16}H_{14}$ | 1,4-Diphenyl-2-butyne | 6 | 60 | 490a, b, c |
| | 2,2'-Dimethyldiphenyl-acetylene | 3 | 8 | 164 |
| | 2,2'-Dimethyldiphenyl-acetylene | 2 | 90-95 | 200 |
| | 3,3'-Dimethyldiphenyl-acetylene | 2 | 89 | 200 |
| | 4,4'-Dimethyldiphenyl-acetylene | 1 | — | 491 |
| | 4,4'-Dimethyldiphenyl-acetylene | 2 | 85-95 | 200 |
| $C_{16}H_{14}O_2$ | 2,2'-Dimethoxydiphenyl-acetylene | 5 | Quant. | 196, 198b |
| | 2,2'-Dimethoxydiphenyl-acetylene | 2 | — | 200 |
| | 3,3'-Dimethoxydiphenyl-acetylene | 2 | — | 200 |
| | 4,4'-Dimethoxydiphenyl-acetylene | 1 | 80 | 201, 198c, 492 |
| | 4,4'-Dimethoxydiphenyl-acetylene | 2 | 90-95 | 200 |
| $C_{16}H_{14}S_2$ | <i>bis</i> (<i>p</i> -Tolylmercapto)-acetylene | 1 | — | 213 |
| | <i>bis</i> (Benzylmercapto)-acetylene | 1 | — | 478 |
| $C_{16}H_{26}$ | 1,15-Hexadecadiyne | 1 | — | 455 |
| | 6,9-Hexadecadiyne | 3 | 15 | 179 |
| $C_{16}H_{23}O_2$ | 7-Hexadecynoic acid | 1 | — | 493 |
| $C_{16}H_{20}$ | 1-Hexadecyne | 1 | — | 17, 81, 494 |
| | 1-Hexadecyne | 2 | 65 | 40 |
| | 2-Hexadecyne | 1 | — | 17, 468, 495 |
| C₁₇ | | | | |
| $C_{17}H_{12}$ | 1,5-Diphenyl-1,4-pentadiyne | 3 | 10 | 176 |
| $C_{17}H_{12}O_2$ | 2,5-Diphenyl-2-penten-4-ynoic acid | 1 | — | 496 |
| $C_{17}H_{24}O_2$ | 3-(8-Nonyl)veratrole | 4 | 51 | 497 |
| $C_{17}H_{23}$ | 7,10-Heptadecadiyne | 3 | 18 | 179 |
| $C_{17}H_{20}$ | Cycloheptadecyne | 1 | — | 490 |
| C₁₈ | | | | |
| $C_{18}H_{12}$ | β -Naphthylphenyl-acetylene | 1 | 58 | 15 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|-------------------|--|--------|---------|--|
| $C_{18}H_{18}$ | β -Naphthylphenyl-acetylene (<i>Continued</i>) | 5 | — | 197 |
| | 4,4'-Diethyldiphenyl-acetylene | 2 | 73 | 200 |
| | 3,4,3',4'-Tetramethyldiphenyldiacetylene | 2 | 90-95 * | 200 |
| $C_{18}H_{18}O_2$ | 4,4'-Diethoxydiphenyl-acetylene | 1 | — | 198c |
| $C_{18}H_{18}O_4$ | 3,4,3',4'-Tetramethoxydiphenylacetylene | 1 | 45-50 | 199 |
| $C_{18}H_{18}O_2$ | 5-Octadecynoic acid | 1 | — | 498 |
| | 6-Octadecynoic acid | 1 | — | 498, 499, 500, 501, 502, 503, 504, 505 |
| | 7-Octadecynoic acid | 1 | — | 498 |
| | 8-Octadecynoic acid | 1 | — | 503 |
| | 9-Octadecynoic acid | 1 | 33-42 | 506, 507, 508, 509, 228a |
| | 10-Octadecynoic acid | 1 | — | 503 |
| | 12-Hydroxy-9-octadecynoic acid | 1 | — | 510, 511, 512, 513 |
| | 1-Octadecyne | 1 | — | 17 |
| | | 4 | — | 136c |
| $C_{18}H_{34}$ | 2-Octadecyne | 1 | — | 17, 468 |
| | 9-Octadecyne | 4 | 15 | 188 |

 $C_{17}-C_{40}$

| | | | | |
|-------------------|------------------------------------|---|-------|--------------------|
| $C_{19}H_{18}$ | 1-Nonadecyne | 2 | 73 | 514 |
| $C_{20}H_{22}$ | 4,4'-Di-n-propyldiphenyl-acetylene | 2 | 55 | 200 |
| | Dimesitylacetylene | 1 | — | 515 |
| | 11-Eicosynoic acid | 1 | — | 493 |
| $C_{20}H_{22}O_2$ | 1,3,3-Triphenyl-1-propyne | 3 | 80 | 162 |
| $C_{21}H_{18}$ | Di-1-naphthylacetylene | 5 | — | 196 |
| $C_{22}H_{24}$ | 4,4'-Di-n-butyldiphenyl-acetylene | 2 | 55 | 200 |
| | 13-Docosynoic acid | 1 | 75-90 | 516, 517, 518, 508 |
| $C_{22}H_{40}O_2$ | 5,5,5-Triphenyl-1-penten-3-yne | 3 | 71 | 519 |
| $C_{23}H_{26}O_2$ | 3-(8-Pentadecynyl)veratrol | 4 | 85 | 497 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

| Formula | Compound | Method | Yield % | References * |
|--------------------|---|--------|---------|--------------|
| $C_{23}H_{40}$ | 10,13-Tricosadiyne | 3 | Poor | 179 |
| $C_{25}H_{18}$ | 4,4'-Diphenyldiphenyl-acetylene | 2 | 91 * | 200 |
| $C_{27}H_{20}$ | 1,3,3,3-Tetraphenyl-1-propyne | 3 | 60-70 | 162 |
| $C_{25}H_{18}Br_4$ | 1,1,4,4-Tetra- <i>p</i> -bromophenyl-2-butyne | 5 | Poor | 207 |
| $C_{25}H_{18}Cl_4$ | 1,1,4,4-Tetra- <i>p</i> -chlorophenyl-2-butyne | 5 | 13 | 207 |
| $C_{25}H_{22}$ | 1,1,4,4-Tetraphenyl-2-butyne | 3 | 40-50 | 162 |
| $C_{23}H_{14}O_4$ | Di-2-anthraquinonyl-acetylene | 5 | — | 207 |
| | | 1 | 89 | 205 |
| $C_{20}H_{22}$ | 1-Phenyl-3,3,3-tri- <i>p</i> -tolyl-1-propyne | 5 | — | 206 |
| | | 3 | 80 | 162 |
| $C_{22}H_{20}$ | 1,1,4,4-Tetra- <i>p</i> -tolyl-2-butyne | 5 | — | 207 |
| $C_{22}H_{20}O_4$ | 1,1,4,4-Tetra- <i>p</i> -methoxyphenyl-2-butyne | 5 | — | 207 |
| $C_{22}H_{20}O_4$ | 1,1,4,4-Tetra- <i>p</i> -ethoxyphenyl-2-butyne | 5 | 35 | 207 |
| $C_{49}H_{30}$ | 1,1,1,4,4,4-Hexaphenyl-2-butyne | 3 | 20-25 | 162 |

See p. 52 for explanation of symbols and methods in this table.

* References 233-519 are listed on pp. 72-78.

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CHAPTER 2

CYANOETHYLATION

HERMAN ALEXANDER BRUSON *

Resinous Products and Chemicals Company

Rohm and Haas Company, Inc.

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* Present address, Industrial Rayon Corporation, Cleveland, Ohio.

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NATURE OF THE REACTION

A variety of organic and inorganic compounds possessing labile hydrogen atoms add readily to acrylonitrile with the formation of molecules containing a cyanoethyl grouping ($-\text{CH}_2\text{CH}_2\text{CN}$). This reaction is commonly known as "cyanoethylation" and resembles closely a Michael type of addition.



Typical compounds containing reactive hydrogen atoms which have been added to acrylonitrile are as follows:

I. Compounds having one or more $-\text{NH}-$ groups such as ammonia, primary and secondary amines, hydrazine, hydroxylamine, imides, lactams, and amides.

II. Compounds having one or more $-\text{OH}$, $-\text{SH}$, or $-\text{AsH}-$ groups such as water, alcohols, phenols, oximes, hydrogen sulfide, mercaptans, and arsines.

III. Certain acidic compounds, other than carboxylic acids, such as hydrogen cyanide, hydrogen chloride, hydrogen bromide, hypochlorous acid, and sodium bisulfite.

IV. Compounds possessing the grouping HCX_3 in which X is chlorine or bromine.

V. Sulfones having a $-\text{CH}_2-$ group between the $-\text{SO}_2-$ group and an olefinic linkage or an aromatic ring.

VI. Nitro compounds having a $-\text{CH}-$, $-\text{CH}_2-$, or CH_3- group contiguous to the $-\text{NO}_2$ group.

VII. Ketones or aldehydes having a $-\text{CH}-$, $-\text{CH}_2-$, or CH_3- group contiguous to the carbonyl group.

VIII. Compounds such as malonic esters, malonamide, cyanoacetamide, etc., in which a $-\text{CH}-$ or $-\text{CH}_2-$ group is situated between $-\text{CO}_2\text{R}$, $-\text{CN}$, or $-\text{CONH}-$ groups.

IX. Compounds such as benzyl cyanide or allyl cyanide in which a $-\text{CH}_2-$ group is situated between a cyano group and an aryl nucleus or an ethylenic linkage.

X. Compounds in which a $-\text{CH}-$ or $-\text{CH}_2-$ group is situated between two ethylenic carbon atoms of a carbocycle or of a heterocycle, such as cyclopentadiene, indene, fluorene, and 2-phenylindole.

The cyanoethylation reaction, except with certain amines, usually requires the presence of an alkaline catalyst. Typical catalysts which are useful for the purpose are the oxides, hydroxides, alkoxides, hydrides, cyanides, and amides of the alkali metals sodium and potassium, as well as the alkali metals themselves. The strongly basic quaternary ammonium hydroxides, in particular benzyltrimethylammonium hydroxide (Triton B), are particularly effective because of their solubility in organic media. Only small amounts of catalyst are required; usually from 1% to 5% of catalyst based on the weight of the acrylonitrile is sufficient. The cyanoethylation of certain amines requires an acidic catalyst.

Many of the reactions are strongly exothermic and require cooling to prevent excessive polymerization of the acrylonitrile. Inert solvents such as benzene, dioxane, pyridine, or acetonitrile are often useful to dissolve solid reactants or to moderate the reaction. *tert*-Butyl alcohol, although reactive with acrylonitrile at temperatures above 60° , is relatively inert at or near room temperature and is often useful as a solvent since it dissolves appreciable amounts of potassium hydroxide (up to about 4% at 25°) to give an effective catalyst solution.

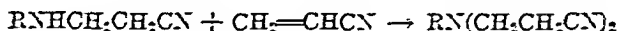
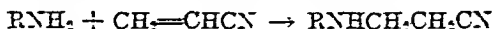
In order to prevent sudden reactions which may get out of control, it is advisable to dissolve or disperse the catalyst in the hydrogen donor, with or without the use of an auxiliary solvent, and to add the acrylonitrile gradually with mechanical stirring while controlling the temperature of the reaction.

SCOPE AND LIMITATIONS

It is most convenient to discuss the scope and limitations of the cyanoethylation reaction in terms of the different classes of compounds which add to acrylonitrile. This is done in the subsections which follow.

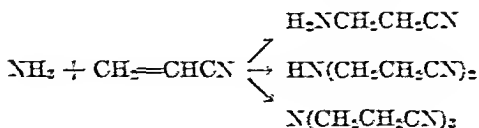
Cyanoethylation of Ammonia and Amines (Tables I-IV)

Ammonia and most amines add to acrylonitrile without the aid of a catalyst.¹ In general, amines add more readily than any other class of compounds, but the ease of addition varies considerably. With those amines which react slowly an acidic or basic catalyst is desirable, and with some amines a catalyst is essential. Primary amines may react with one or two moles of acrylonitrile. Low temperatures favor the addition of one molecule of amine with formation of a secondary amine, an alkylcyanoethylamine; higher temperatures result in the addition of the initial secondary amine to a second molecule of acrylonitrile with formation of a tertiary amine, an alkyl-dicyanoethylamine, especially if excess of acrylonitrile is present. Since secondary amines can yield



only a single product with acrylonitrile the temperature at which the reaction takes place may be varied over a wide range.

Ammonia yields a mixture of mono-, di-, and tri-cyanoethylation products,^{1,2,3} though the last is formed much less readily than the other two.



The yield of the three cyanoethylamines depends upon the proportions of the reactants and the temperature. When five moles of anhydrous liquid ammonia is heated with four moles of acrylonitrile in an autoclave at 90° for thirty minutes, β -aminopropionitrile is obtained in only 12.5% yield, whereas the disubstituted amine, bis(2-cyanoethyl)amine, is obtained in about 75% yield.¹ If the molar ratio of liquid ammonia

¹ Hoffmann and Jacob, U. S. pat. 1,992,615 [*C.A.*, 29, 2548 (1935)].

² Whitmore, Mosher, Adams, Taylor, Chapin, Weissel, and Yanko, *J. Am. Chem. Soc.*, 66, 725 (1944).

³ Wiedemann and Montgomery, *J. Am. Chem. Soc.*, 67, 1994 (1945).

to acrylonitrile is 8:1, a 22% yield of β -aminopropionitrile and a 64% yield of the secondary amine can be obtained³ by reaction at 40°. If one mole of acrylonitrile is gradually added to one mole of concentrated aqueous ammonia at a temperature between 30° and 35°, and the mixture is allowed to stand for three hours, *bis*(2-cyanoethyl)amine can be obtained in 85% yield by distilling the product in vacuum. On the other hand, rapid addition of acrylonitrile below the surface of an excess of aqueous ammonia preheated to 110° followed by a short reaction period and rapid cooling gives β -aminopropionitrile in more than 60% yield.⁴

An extensive study of the reaction of aqueous ammonia with acrylonitrile⁵ has shown, as would be predicted on theoretical grounds, that increasing the ratio of aqueous ammonia to acrylonitrile favors formation of the primary amine. When the molar ratio of aqueous ammonia to acrylonitrile is 20:1 and cooling is employed, a 39% yield of the primary amine and a 39% yield of the secondary amine can be secured.⁵ By operating without cooling and under pressure the exothermic reaction carries the temperature to 71°, and, under these conditions, a molar ratio of 7.5 moles of aqueous ammonia to one mole of acrylonitrile yields 38.3% of the primary amine and 53.2% of the secondary amine.

At higher temperatures hydrolysis and disproportionation of the various aminopropionitriles occur. At 150° aqueous ammonia and acrylonitrile yield 35% of β -aminopropionic acid after eight hours.⁶ It has also been pointed out by Kirk⁷ that β -aminopropionic acid is formed upon heating *bis*(2-cyanoethyl)amine with aqueous ammonia at 200° in an autoclave; and Kung⁸ has shown that β -aminopropionitrile is formed by pyrolysis of *bis*(2-cyanoethyl)amine or *tris*(2-cyanoethyl)-amine.

Methylamine adds to acrylonitrile in the cold to give a 78% yield of β -methylaminopropionitrile;⁹ even in the presence of methanol, which itself adds to acrylonitrile when alkaline catalysts are used, the amine adds readily. Upon heating methylamine and acrylonitrile in a sealed tube at 80° for six hours, the di-cyanoethylation product is formed.⁹

Ethylamine with an equimolar quantity of acrylonitrile below 30° gives a 90% yield of β -ethylaminopropionitrile.³ When heated with excess acrylonitrile, a 60% yield of *bis*(2-cyanoethyl)ethylamine³ is obtained. Similarly, *n*-propylamine and isopropylamine give, respec-

⁴ Ford, Buc, and Greiner, *J. Am. Chem. Soc.*, **69**, 545 (1947).

⁵ Buc, Ford, and Wise, *J. Am. Chem. Soc.*, **67**, 92 (1945).

⁶ Carlson and Hotchkiss, U. S. pat. 2,335,997 [C.A., **33**, 2972 (1944)]; U. S. pat. 2,377,401 [C.A., **39**, 4333 (1945)].

⁷ Kirk, U. S. pat. 2,334,163 [C.A., **33**, 2667 (1944)].

⁸ Kung, U. S. pat. 2,401,429 [C.A., **40**, 5447 (1946)].

⁹ Cook and Reed, *J. Chem. Soc.*, 1945, 399.

tively, 92% and 95% yields of *n*-propylaminopropionitrile¹⁰ and isopropylaminopropionitrile;¹¹ *n*-butylamine, *sec*-butylamine, and *tert*-butylamine give 98%, 83%, and 56% yields, respectively, of the mono-cyanoethylated derivatives.¹⁰ In general, small amounts of the di-cyanoethylated compounds are obtained as by-products.

Piperidine is a very reactive secondary amine and adds to acrylonitrile with evolution of heat.^{2,12} Morpholine is only slightly less reactive.² Diethylamine, however, adds more slowly than morpholine, although no difficulty is encountered in obtaining a nearly quantitative yield of product merely by heating the reactants together.² Di-*n*-propylamine gives a 90% yield of the cyanoethylation product, but diisopropylamine gives only a 12% yield; di-*n*-butylamine gives a 96% yield, and diisobutylamine a 51% yield.

The rate of addition of dialkylamines decreases progressively with the size of the alkyl groups.² For example, an equimolar mixture of acrylonitrile and di-*n*-amylamine when warmed to 50° and allowed to stand overnight gives a 60% yield of β -di-*n*-amylaminopropionitrile,¹³ whereas di-*n*-octylamine does not react with excess of acrylonitrile at 50° and requires a temperature of 100° to give an 80% yield of β -di-*n*-octylaminopropionitrile after one hundred hours.¹⁴ A branched-chain octylamine reacts more slowly than the straight-chain isomer; *bis*(2-ethylhexyl)amine and excess of acrylonitrile under the conditions just specified give a 65% yield of β -*bis*(2-ethylhexyl)aminopropionitrile,¹⁴ and a 77% yield after three hundred and sixty hours at 100°. These results indicate that the rate of addition is primarily dependent upon the size and complexity of the amine.² The basicity of the amine is probably not an important factor since the ionization constants of diethylamine, piperidine, and morpholine are, respectively, 1.2×10^{-3} , 1.6×10^{-3} , and 2.4×10^{-6} , and all three react quite rapidly.¹⁴

The reversibility of cyanoethylation reactions, mentioned in the discussion of the reaction of ammonia and acrylonitrile, is again illustrated by the gradual decomposition of the higher β -dialkylaminopropionitriles to dialkylamine and acrylonitrile or its polymer when heated near their boiling points. Cyanoethyldiethanolamine upon distillation yields diethanolamine and a polymer of acrylonitrile.² Similarly, cyanoethylcyclohexylamine gives 20% of cyclohexylamine.¹ It has also been observed that when equimolar amounts of secondary amine and acrylo-

¹⁰ Tarbell, Shakespear, Claus, and Bunnett, *J. Am. Chem. Soc.*, **68**, 1217 (1946).

¹¹ Pearson, Jones, and Cope, *J. Am. Chem. Soc.*, **68**, 1227 (1946).

¹² Terentev and Terenteva, *J. Gen. Chem. U.S.S.R.*, **12**, 415 (1942) [*C.A.*, **37**, 3095 (1943)].

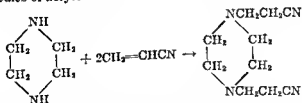
¹³ Holcomb and Hamilton, *J. Am. Chem. Soc.*, **64**, 1309 (1942).

¹⁴ Burckhalter, Jones, Holcomb, and Sweet, *J. Am. Chem. Soc.*, **65**, 2014 (1943).

nitrile react some of the unreacted starting materials are always recovered; the yield is never so high as when an excess of one of the reactants is used.²

The cyanoethylation reaction has been extended to many more complex primary and especially secondary amines. Thus, benzylamine gives $C_6H_5CH_2NHCH_2CH_2CN$; ¹⁵ γ -diethylaminopropylamine gives a 79% yield of $(C_2H_5)_2NCH_2CH_2CH_2NHCH_2CH_2CN$ and a 9% yield of $(C_2H_5)_2NCH_2CH_2CH_2N(CH_2CH_2CN)_2$; β -morpholinoethylamine gives $OC_4H_8NCH_2CH_2NHCH_2CH_2CN$ in 81.5% yield.² Hydrazine hydrate and acrylonitrile in equimolar quantities react in the cold to form $NH_2NHCH_2CH_2CN$ in 90% yield,¹ and hydroxylamine gives an almost quantitative yield of $HONHCH_2CH_2CN$.¹ At 95° such mixed secondary amines as methyl-*n*-propylamine, ethylisopropylamine, cyclopentylethylamine, *sec*-butyl-*n*-propylamine, *n*-butyl-*sec*-butylamine,¹⁶ and benzylmethylamine¹⁵ add readily to acrylonitrile. The cyclic bases pyrrolidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, and 2,6-dimethylpiperidine are other examples of amines which add readily.¹⁷ The cyclic imine, 2,2-dimethylethyleneimine, when refluxed for thirty hours with acrylonitrile gives 1-(2-cyanoethyl)-2,2-dimethylethyleneimine in 66% yield.¹⁸ Such alkanolamines as ethanolamine, diethanolamine, propanolamine, and *N*-methyl-*N*-ethanolamine¹⁴ are preferentially cyanoethylated on the basic nitrogen atom rather than on the hydroxyl group.¹⁹

Heterocyclic bases containing two imino groups, such as piperazine, hydrogenated pyrimidines, and hydrogenated perimidines, react with two molecules of acrylonitrile.^{20,21}



Certain amines, especially those in the aromatic and heterocyclic series, react only very slowly with acrylonitrile in the absence of a catalyst. Methylaniline and 1,2,3,4-tetrahydroquinoline do not react appreciably

¹⁵ King and McMillan, *J. Am. Chem. Soc.*, **68**, 1468 (1946).

¹⁶ Corse, Bryant, and Shonle, *J. Am. Chem. Soc.*, **68**, 1906 (1946).

¹⁷ Corse, Bryant, and Shonle, *J. Am. Chem. Soc.*, **68**, 1912 (1946).

¹⁸ Tarbell and Fukushima, *J. Am. Chem. Soc.*, **68**, 2501 (1946).

¹⁹ Hoffmann and Jacobl, U. S. pat. 2,017,537 [*C.A.*, **29**, 8003 (1935)].

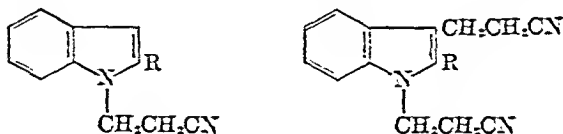
²⁰ I. G. Farbenind. A.-G., Brit. pat. 457,621 [*C.A.*, **31**, 3068 (1937)].

²¹ Behr, Kirby, MacDonald, and Todd, *J. Am. Chem. Soc.*, **68**, 1297 (1946).

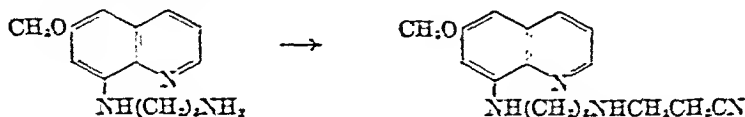
with acrylonitrile when heated in a sealed tube at 200° ,² but in the presence of glacial acetic acid (about 5% of the weight of the amine) they react at 120 – 140° to give good yields of the cyanoethylated derivatives. Cyanoethylation of *n*-butylcresidine, 2-methylindoline, 1,2,3,4-, 10,11-hexahydrocarbazole,²³ and *p*-anisidine²³ is accelerated by acetic acid as catalyst. Bases appear to be ineffective as catalysts with this group of substances.²

Other acidic catalysts that have been proposed for the cyanoethylation of otherwise unreactive amines are oxalic acid, formic acid, chloroacetic acid, sulfuric acid, and salts of nickel, zinc, cobalt, copper, or other metals capable of forming ammoniates; the ammonia or amine salts of strong mineral acids are also successful catalysts.^{1,2,22} Copper salts, in particular copper chloride, sulfate, oleate, borate, or acetate, appear to inhibit the polymerization of acrylonitrile at elevated temperatures and to result in an improvement of yields.²²

Alkaline catalysts have been very widely employed. Heterocyclic bases such as pyrrole, carbazole, indole, dihydroacridine, decahydroquinoline, perimidine, and thiodiphenylamine are cyanoethylated smoothly in the presence of small amounts of sodium ethoxide.²³ The same catalyst is effective in the cyanoethylation of benzimidazole at room temperature in pyridine as a solvent.²³ α -Methylindole and α -phenylindole react with acrylonitrile when heated in the presence of sodium methoxide and copper borate to yield mono- and di-cyanoethylated products.²³ The second cyanoethyl group is introduced as a result of addition involving the active hydrogen in the 3-position.



Aqueous potassium hydroxide is a catalyst for cyanoethylation of 8-(3-aminopropylamino)-6-methoxyquinoline at room temperature.²⁴



²² I.G. Farbenind. A.-G., Brit. pat. 466,316 [C.A., 31, 7887 (1937)].

²³ Elderfield, Gensler, Bembry, Kremer, Brody, Hageman, and Head, *J. Am. Chem. Soc.* 68, 1262 (1946).

²⁴ Kissinger, Von, and Carmack, *J. Am. Chem. Soc.*, 68, 1563 (1946).

Triton B as a catalyst²⁵ permits cyanoethylation of carbazole even at ice-bath temperature;² heterocyclic bases, such as isatin,²⁶ pyrrole, 2-phenylindole, 2-phenyl-3-indolecarboxaldehyde, 3-indolecarboxaldehyde, and 2-methyl-3-indolecarboxaldehyde, are readily cyanoethylated on the nitrogen atom at moderate temperatures with this catalyst.²⁷ Triton B has proved useful as a catalyst in cyanoethylation of 2,3-dimethylpiperidine,¹⁷ 2,4-dimethylpiperidine,¹⁷ methylisopropylamine, *n*-butylmethylamine, *sec*-butylmethylamine, isobutylmethylamine, methyl-2-pentylamine, methyl-3-pentylamine, cyclopentylmethylamine, 2,3-dimethylbutylamine, 2,4-dimethylpentylamine, 4-methylheptylamine, ethylisobutylamine, isopropyl-*n*-propylamine, isobutyl-*n*-propylamine, and cyclopentyl-*n*-butylamine.¹⁶

Cyanoethylation of Amides, Imides, and Lactams (Table V)

The cyanoethylation of amides, imides, and lactams has been described by Wegler.²⁸ The addition of compounds of these classes to acrylonitrile takes place readily and can be considered very general. Amides may react with one or two moles of acrylonitrile. *N*-Alkyl acid amides, with an occasional exception, yield the expected products, as do imides and lactams. Aromatic and aliphatic sulfonamides have not been extensively studied, but some of them add to acrylonitrile in the same way as acid amides. Alkaline catalysts are employed.

The addition of formamide to acrylonitrile occurs readily in the presence of alkaline catalysts such as sodium or sodium hydroxide. At moderate temperatures and with an excess of formamide the reaction readily yields β -formylaminopropionitrile. At temperatures of 85° or higher, and particularly with an excess of acrylonitrile, di-cyanoethylation predominates to yield β -formyliminodipropionitrile.



Formamide also can react with more than two moles of acrylonitrile;²⁹ a substance with five to six moles of combined acrylonitrile has been reported but the structure is not known. *N*-Methylformamide is not cyanoethylated even in the presence of alkali catalysts although the corresponding *N*-*n*-propyl-, *N*-*n*-butyl-, *N*-*n*-hexyl-, cyclohexyl-, and *N*-phenylformamides add easily to acrylonitrile.³⁰ It has been suggested

²⁵ Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

²⁶ DiCarlo and Lindwall, *J. Am. Chem. Soc.*, **67**, 199 (1945).

²⁷ Blume and Lindwall, *J. Org. Chem.*, **10**, 253 (1945).

²⁸ Wegler, Ger. pat. 734,725 [C.A., **33**, 3671 (1941)].

²⁹ Wegler, Ger. pat. 735,771 [C.A., **33**, 3992 (1944)].

³⁰ Wegler, Report to I G. Farbenfabr. A.-G., April 21, 1941 (captured enemy documents).

that methylformamide is sufficiently acidic to neutralize the alkaline catalysts and render them ineffective.²⁰ N-Butylformamide will react with as many as four moles of acrylonitrile to give a product of unknown structure.

Acetamide in excess gives good yields of β -acetaminopropionitrile.²⁰ It shows less tendency than formamide to react with two moles of acrylonitrile. In contrast to methylformamide, the cyanoethylation of N-methylacetamide proceeds satisfactorily. Similarly, N-methylpropionamide in the presence of 0.5% by weight of sodium hydroxide is smoothly cyanoethylated at 70–80° to yield $\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CN}$.²¹ Benzamide and acetanilide react with one mole of acrylonitrile at 90–100° in a little dioxane and in the presence of 1% of sodium hydroxide as a catalyst.²¹ Under similar conditions, N,N'-bis-methyladipamide yields the di-cyanoethylation product $\text{NCCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CO}(\text{CH}_2)_4\text{CON}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CN}$. Crotonamide²² yields the di-cyanoethylation product $\text{CH}_3\text{CH}=\text{CHCON}(\text{CH}_2\text{CH}_2\text{CN})_2$, instead of the product $\text{CH}_2=\text{CHC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{CONH}_2$ previously reported.²³

The cyanoethylation of most imides and lactams proceeds at 90–95° in the presence of 1–2% of sodium hydroxide as a catalyst²³ to yield the corresponding N-(2-cyanoethyl) derivatives. Galat²⁴ obtained a quantitative yield of N-(2-cyanoethyl)phthalimide by refluxing phthalimide and acrylonitrile for ten minutes in the presence of a small amount of Triton B. Succinimide and phthalimide in a little dioxane at 95° with 1–2% of sodium hydroxide as a catalyst react to form the corresponding N-(2-cyanoethyl)imides.²³ α -Pyrrolidone,²³ ω -caprolactam,²³ and 2-pyridone²⁵ may be cyanoethylated in the presence of alkaline catalysts such as sodium hydroxide or potassium carbazole.

Certain sulfonamides can be cyanoethylated in the same way. Benzenesulfonamide and acrylonitrile, regardless of the relative amounts of reactants, form primarily the di-cyanoethylation product, $\text{C}_6\text{H}_5\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$. *p*-Acetaminobenzenesulfon-N-methylamide is readily cyanoethylated on the sulfonamide group. *p*-Acetaminobenzenesulfon-



N,N-dimethylamide, $\text{CH}_3\text{CONHC}_6\text{H}_4\text{SO}_2\text{N}(\text{CH}_3)_2$, could not be cyanoethylated on the NH— group, even though acetanilide can be cyanoethylated. The influence of the sulfonamide group on a *p*-amino group is shown also by the failure of the amino group in *p*-aminobenzenesulfon-

²⁰ I.G. Farbenind. A.-G., Fr. pat. 577,120 (1942).

²¹ Brown, unpublished work.

²² Brown and Rieker, *J. Am. Chem. Soc.*, **65**, 18 (1943).

²³ Galat, *J. Am. Chem. Soc.*, **67**, 1414 (1945).

²⁴ Adams and Jones, *J. Am. Chem. Soc.*, **69**, 1504 (1947).

N,N-dimethylamide to cyanoethylate. Saccharin also resists cyanoethylation.

Some aliphatic sulfonamides have been studied; propanesulfon-N-methylamide yields $\text{CH}_3\text{CH}_2\text{CH}_2\text{SO}_2\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})$ almost quantitatively, whereas propanesulfonamide is reported not to add to acrylonitrile. Benzyl sulfonamide reacts with acrylonitrile in the presence of Triton B to yield N,N-bis(2-cyanoethyl)benzylsulfonamide,²⁸ $\text{C}_6\text{H}_5\text{CH}_2\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$, and not a product with cyanoethyl groups on the methylene carbon atom as was first suggested.²⁷ The cyanoethylation of aliphatic sulfonamides has been patented by McQueen.²⁸

Cyanoethylation of Water and Alcohols (Tables VI-VIII and XIII)

Water reacts with acrylonitrile^{27,28,29} in the presence of alkaline catalysts to give β,β' -dicyanoethyl ether, $\text{NCCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$. Ethylene cyanohydrin is probably an intermediate in this reaction.

Practically all primary and secondary alcohols react with acrylonitrile in the presence of alkaline catalysts to form cyanoethyl ethers. The



reactions take place at or below room temperature with the lower aliphatic alcohols, particularly when the more active basic catalysts such as sodium, sodium methoxide, sodium or potassium hydroxide, or Triton B are used. Usually 0.5% to 5% of catalyst based on the weight of alcohol is adequate. The presence of other functional groups such as dialkylamino, halogen, olefinic, ether, or cyano does not interfere with the reaction. Glycols and polyalcohols are readily poly-cyanoethylated. Tertiary alcohols, on the other hand, react with difficulty or not at all. It has been demonstrated, however, that ethynyl tertiary alcohols react readily, the acetylene linkage apparently activating the addition reaction. Only the esters of hydroxy acids have resisted cyanoethylation; attempts to add ethyl glycolate, ethyl lactate, and ethyl ricinoleate to acrylonitrile have failed.

Most of the simple aliphatic alcohols can be cyanoethylated at 35–60° in the presence of 0.5–1% of sodium or sodium hydroxide. Examples are methanol,²⁸ ethanol,^{28,29} 2-propanol,²⁸ allyl alcohol,²⁸ n-amyl alcohol,²⁸

²⁷ Bruson and Riener, *J. Am. Chem. Soc.*, **70**, 213 (1948).

²⁸ Bruson and Riener, *J. Am. Chem. Soc.*, **65**, 23 (1943).

²⁹ McQueen, U. S. pat. 2,424,664 (1947).

³⁰ Bruson, U. S. pat. 2,382,036 [C.A., **40**, 347 (1946)].

³¹ Hopff and Rapp, Ger. pat. 731,708 [C.A., **33**, 535 (1940)].

³² American Cyanamid Co., Brit. pat. 544,421 [C.A., **36**, 6543 (1942)].

³³ Koelsch, *J. Am. Chem. Soc.*, **65**, 437 (1943).

2-ethylhexanol,⁴¹ dodecanol,⁴¹ and octadecanol.⁴¹ *n*-Butyl alcohol and acrylonitrile react rapidly at 40° with 0.4% of sodium as a catalyst.⁴² Triton B^{43,44,45} has been used effectively for cyanoethylation of these simple alcohols as well as of more complex ones. Tertiary amines have also been reported as satisfactory catalysts.⁴⁶

Various methods for cyanoethylating aliphatic alcohols have been evaluated by MacGregor and Pugh.⁴⁵ As a general procedure for all aliphatic alcohols, including the long-chained alcohols, it is recommended that acrylonitrile be added to a solution of 0.05% of sodium in the alcohol at room temperature and that the reaction be completed at 80°. For alcohols with not more than five carbon atoms, two other procedures are reported as satisfactory: (1) equimolar quantities of acrylonitrile and alcohol are shaken at room temperature with a 2% aqueous sodium hydroxide solution as catalyst; (2) an equimolecular quantity of acrylonitrile is gradually added with cooling and stirring to a solution of 0.5% of potassium hydroxide in the alcohol. After the exothermic reaction is over, the reaction mixture is heated at 80° on a steam bath until refluxing ceases. Yields of 80–90% result.

The cyanoethylation of alcohols is an equilibrium reaction. The position of the equilibrium is more favorable to the addition product with primary than with secondary alcohols. Thus, 2-propanol gives a lower yield (69%) of cyanoethylation product than methanol, ethanol, or 1-butanol, which give 89%, 78%, and 86% yields, respectively.⁴⁴ Caution must be observed in the isolation of the β -alkoxypropionitriles by distillation, particularly those derived from secondary alcohols or from primary alcohols with more than seven carbon atoms. The alkaline catalyst must be destroyed by acidification or neutralization since the products are readily dissociated by heat in the presence of alkalis into the original alcohol and a polymer of acrylonitrile.⁴³

Tertiary alcohols have not been extensively studied. *tert*-Butyl alcohol does not react with acrylonitrile at 30–40° and can, therefore, be used as a solvent for many cyanoethylation reactions which take place at low temperatures. At 80°, however, it reacts with acrylonitrile in the presence of 2% by weight of sodium hydroxide to form β -(*tert*-butoxy)propionitrile.⁴¹ An acetylenic linkage attached to the tertiary alcohol carbon activates the addition. Thus, ethynyl dimethyl carbinol in the presence of sodium methoxide adds readily to acrylonitrile at 20°

⁴¹ I.G. Farbenind. A.-G., Fr. pat. 796,001 [C.A., 30, 5590 (1936)].

⁴² Utermohlen, *J. Am. Chem. Soc.*, 67, 1505 (1945).

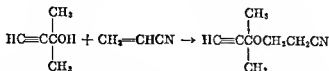
⁴³ Brunson, U. S. pat. 2,289,791 [C.A., 35, 5359 (1942)].

⁴⁴ Brunson, U. S. pat. 2,289,792 [C.A., 36, 5559 (1942)].

⁴⁵ Clifford and Liskay, Can. pat. 415,525 [C.A., 38, 979 (1944)].

⁴⁶ MacGregor and Pugh, *J. Chem. Soc.*, 1945, 535.

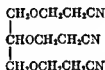
to yield the expected ether.⁴³ Acetylenic hydrogen atoms of acetylene,



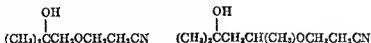
alkylacetylenes, or phenylacetylene do not react with acrylonitrile under the usual cyanoethylating conditions.

A wide variety of alcohols of the arylaliphatic,⁴⁴ alicyclic,^{44,45} and heterocyclic series⁴⁴ are readily cyanoethylated. For illustration may be mentioned benzyl alcohol,⁴⁴ cyclohexanol,⁴⁵ 3,4-dimethylcyclohexanol,⁴⁴ and menthol.⁴⁵

Primary and secondary, but not tertiary, hydroxyl groups in glycols and polyhydric alcohols are cyanoethylated.^{41,49-52} Glycol is di-cyanoethylated in more than 80% yield; trimethylene, pentamethylene, and decamethylene glycols^{37,50} also react readily. 1,4-Pentanediol gives an 83% yield of di-cyanoethylation product.⁵³ Glycerol gives a tri-cyanoethyl derivative^{37,50} in 74% yield, and pentaerythritol, mannitol, and sorbitol are reported to be completely cyanoethylated.⁵⁰ A tertiary



alcohol group if present in a glycol resists cyanoethylation.⁵⁰ In isobutylene glycol and 2-methyl-2,4-pentanediol, only the primary or secondary hydroxyl reacts. Polyvinyl alcohol^{44,53} yields products of varying degrees of cyanoethylation.



Many alcohols with ether linkages present react easily. Diethylene glycol,³⁷ triethylene glycol, tetraethylene glycol,⁵⁰ and the higher polyethylene glycols are readily cyanoethylated on one or both hydroxyl

⁴³ Bruson, U. S. pat. 2,280,790 [C.A., 36, 5583 (1942)].

⁴⁴ Bruson, U. S. pat. 2,401,607 [C.A., 40, 5450 (1946)].

⁴⁵ Treppenhauer, König, and Schröter, Ger. pat. 734,475 [C.A., 38, 2966 (1944)].

⁴⁶ Carpenter, U. S. pat. 2,404,164 [C.A., 40, 7232 (1946)].

⁴⁷ Christian, Brown, and Hixon, *J. Am. Chem. Soc.*, 69, 1961 (1947).

⁴⁸ I.G. Farbenind. A.-G., Fr. pat. 830,863 [C.A., 33, 1838 (1939)].

⁴⁹ Houts, U. S. pat. 2,341,553 [C.A., 38, 4347 (1944)].

groups.⁵¹ The mono-methyl, -ethyl, -*n*-butyl, -allyl,⁵² -phenyl, and substituted phenyl ethers of ethylene glycol react normally;⁴⁸ furfuryl alcohol,⁵³ tetrahydrofurfuryl alcohol,⁴⁴ and glyceryl α -ethers⁵⁴ also add to acrylonitrile. Thiodiethylene glycol and acrylonitrile give a good yield of bis(2-cyanoethoxyethyl) sulfide.^{55,57} Sugars,⁵⁴ starch,⁵³ and cellulose^{54,55,56} may be considered in this general class of compounds and have been found to react to give products of various solubilities and other physical properties. When cellulose is refluxed with an excess of acrylonitrile in the presence of 2% aqueous sodium hydroxide, a clear solution is obtained from which dilute ethanol precipitates a white flaky product containing three cyanoethyl groups per glucose unit.⁵² The cyanoethylation of cellulose xanthate and of viscose leads to interesting fibers.⁵⁷

Unsaturated alcohols which have been added to acrylonitrile are numerous. Sodium, sodium hydroxide, and sodium methoxide have normally been used as catalysts. The reaction products from allyl,^{48,58} methallyl,⁵⁹ furfuryl,⁶⁰ oleyl,⁶¹ and cinnamyl alcohols,⁶² geraniol,⁶³ linalool,⁶⁴ citronellol,⁶⁵ and unsaturated ether alcohols⁵⁶ have been described.

The hydroxyl group in cyanohydrins reacts normally with acrylonitrile. Formaldehyde cyanohydrin and acrylonitrile when heated with tributylamine as a catalyst give β -(cyanomethoxy)propionitrile,⁶⁶ $\text{NCCH}_2\text{OCH}_2\text{CH}_2\text{CN}$; lactonitrile gives a corresponding derivative, $\text{CH}_3\text{CH}(\text{CN})\text{OCH}_2\text{CH}_2\text{CN}$.⁶⁷ Ethylene cyanohydrin with sodium, sodium hydroxide,^{57,58,61,62,64} or sodium cyanide⁶⁸ as catalyst gives bis-2-cyanoethyl ether, $\text{NCCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$. The same product can be obtained by the reaction between two moles of acrylonitrile and one mole of water.^{57,61,64}

The halogenated alcohols ethylene chlorohydrin⁴⁸ and β -chloroethoxyethanol⁴⁸ add to acrylonitrile in the presence of a small amount of concentrated aqueous sodium hydroxide to give $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ and $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$, respectively. The ω -fluoroalcohols, $\text{F}(\text{CH}_2)_n\text{OH}$, have also been cyanoethylated with acrylonitrile.⁶⁹

⁵¹ Schroeder, U. S. pat. 2,493,685 [C.A., 40, 6429 (1945)].

⁵² Hurd and Gerbstein, *J. Am. Chem. Soc.*, 69, 2328 (1947).

⁵³ Bock and Honk, U. S. pat. 2,316,128 [C.A., 37, 5812 (1943)].

⁵⁴ Bock and Honk, U. S. pats. 2,332,048 and 2,332,049 [C.A., 38, 1640 (1944)]; U. S. pat. 2,349,787 [C.A., 39, 1291 (1945)].

⁵⁵ Horitz, U. S. pat. 2,375,847 [C.A., 39, 4455 (1945)].

⁵⁶ Hollan and Moss, *J. Ind. Eng. Chem.*, 39, 929 (1947).

⁵⁷ Hamley, U. S. pat. 2,333,782 [C.A., 38, 2349 (1944)].

⁵⁸ Treppenbauser, König, and Bock, Ger. pat. 731,221 [C.A., 38, 1246 (1944)].

⁵⁹ König, Bock, and Treppenbauser, Ger. pat. 738,339 [C.A., 38, 3920 (1944)].

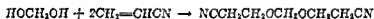
⁶⁰ Hopf, Ger. pat. 743,224 [C.A., 39, 2756 (1945)].

⁶¹ Saunders, *Nature*, 160, 173 (1947).

Tertiary amino alcohols react readily with acrylonitrile when sodium methoxide, sodium hydroxide, or Triton B⁶⁷ is used as catalyst. Diethylaminoethanol¹ gives $(C_2H_5)_2NCH_2CH_2OCH_2CH_2CN$ in 79% yield; 1-diethylamino-4-pentanol² gives $(C_2H_5)_2NCH_2CH_2CH_2CH_2CH_2OCH_2CH_2CN$ in 66% yield; and β -morpholinoethanol gives a 43% yield of $OC_4H_8NCH_2CH_2OCH_2CH_2CN$. Three cyanoethyl radicals are introduced into triethanolamine to give *tris*(2-cyanoethoxyethyl)-amine, $N(CH_2CH_2OCH_2CH_2CN)_3$.⁶⁷

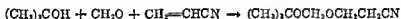
Cyanoethylation of Formaldehyde (Methylene Glycol) (Table X)

Formaldehyde or paraformaldehyde reacts in aqueous solution with acrylonitrile in the presence of alkaline catalysts in the form of the hydrate, $HOCH_2OH$, and cyanoethylation of this intermediate is reported to take place with the formation of the hemiformal of ethylene cyanohydrin or the formal of ethylene cyanohydrin,⁶⁸ depending upon the proportion of reagents.



Only the latter compound has been isolated.

If the reaction between formaldehyde and acrylonitrile is carried out in the presence of an alcohol, the mixed formal of the alcohol and ethylene cyanohydrin results even though the alcohol used is a relatively unreactive tertiary alcohol.⁶⁹ The reactions go smoothly at



35–45° in the presence of aqueous sodium hydroxide or Triton B as catalyst. Similar mixed formals are obtained from formaldehyde and acrylonitrile with such alcohols as methanol, allyl alcohol, benzyl alcohol, and 2-octanol.⁶⁹

Cyanoethylation of Phenols (Table IX)

The reaction of acrylonitrile with the hydroxyl groups of phenols takes place at temperatures in the range of about 120–140°, particularly in the presence of alkaline catalysts such as the alkali metals and alkoxides or tertiary organic bases such as pyridine, quinoline, or dimethylaniline.⁷⁰ When acrylonitrile is gradually added at 130–140° to phenol

⁶⁷ Bruson, U. S. pat. 2,326,721 [C.A., 33, 606 (1944)].

⁶⁸ Walker, U. S. pat. 2,352,671 [C.A., 39, 223 (1945)].

⁶⁹ Bruson, U. S. pat. 2,435,869 (1948).

⁷⁰ Ufer, Ger. pat. 670,357 [C.A., 33, 2907 (1939)].

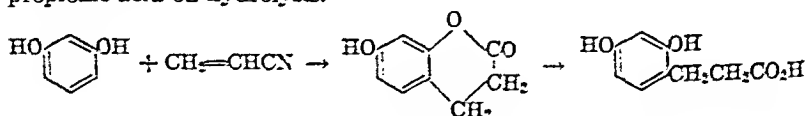
containing 1% by weight of sodium and heating is continued under a reflux condenser for four to six hours at this temperature, a good yield of β -phenoxypropionitrile is obtained.⁷



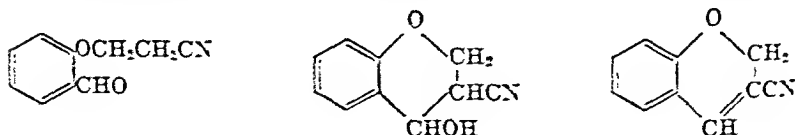
In the same manner *m*-chlorophenol, β -naphthol, various cresols, xyenols, hydroxyanthraquinones, hydroxybiphenyls, hydroxyquinolines, and partially hydrogenated polynuclear phenols such as 5,6,7,8-tetrahydro-1(or 2)-hydroxynaphthalene react with acrylonitrile to yield the corresponding cyanoethyl ethers.⁷ However, the cyanoethylation of β -naphthol in the presence of an *equimolecular amount of sodium hydroxide* suspended in benzene yields 2-hydroxy-1-(2-cyanoethyl)naphthalene in excellent yield.⁷

Polyhydric phenols such as pyrocatechol and hydroquinone can likewise be cyanoethylated in the presence of 1% by weight of sodium at 120–140° to yield the mono-cyanoethyl ether or the di-cyanoethyl ether, depending upon the proportions of acrylonitrile used.⁷

Acrylonitrile is reported to condense with resorcinol in the presence of hydrogen chloride and zinc chloride to yield the lactone of β -(2,4-dihydroxyphenyl)propionic acid which furnishes 2,4-dihydroxyphenylpropionic acid on hydrolysis.⁷



The cyanoethylation of resorcinol in the presence of Triton B gives a 40% yield of 1,3-bis(β -cyanoethoxy)benzene.⁷ Upon refluxing salicylaldehyde with a large excess of acrylonitrile with Triton B as a catalyst, a small yield of 2-(β -cyanoethoxy)benzaldehyde is obtained together with 3-cyano-4-chromanol and 3-cyano-1,2-benzopyran.⁷ In a similar



manner, phenol and *m*-methoxyphenol give 67.5% and 76% yields respectively of β -phenoxypropionitrile and *m*-methoxyphenoxypropionitrile.⁷ Halogenated phenols such as *o*- and *p*-chlorophenol add only

⁷ Hardman, U. S. pat. 2,421,837 [C.A., 41, 5991 (1947)].

⁷ Langley and Adams, *J. Am. Chem. Soc.*, 44, 2326 (1922).

⁷ Bachman and Levine, *J. Am. Chem. Soc.*, 70, 599 (1948).

slowly to acrylonitrile, whereas *p*-nitrophenol and methyl salicylate apparently do not add at all.⁷³ The cyanoethylation of 6-bromo-2-naphthol gives a 10% yield of the corresponding cyanoethyl ether,⁷³ whereas 2-naphthol gives a 79% yield of β -(2-naphthoxy)propionitrile when the reaction is carried out in the presence of Triton B.⁷⁴

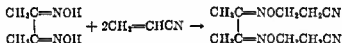
Cyanoethylation of Oximes (Table IX)

The hydroxyl group of aldoximes and ketoximes adds to acrylonitrile in the presence of alkaline catalysts^{27,75} to form oximino ethers in 60–90% yields. The reactions take place at or near room temperature and are exothermic so that cooling and the use of an inert solvent such as dioxane are advisable.

A solution of acetone oxime, cyclohexanone oxime, or furfuraldehyde oxime in dioxane containing a small amount of sodium methoxide reacts smoothly at 25–35° with acrylonitrile to yield the corresponding cyanoethyl ether. Liquid oximes, such as α -ethyl- β -propylacrolein oxime,

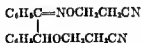


methyl *n*-hexyl ketoxime, and α -ethylhexaldoxime, do not require a solvent. Insoluble oximes such as dimethylglyoxime can be suspended in water containing a small amount of sodium hydroxide and cyanoethylated by gradually adding acrylonitrile.



Acetophenone oxime in benzene containing a small amount of Triton B adds acrylonitrile at 40–50° to give the corresponding cyanoethyl ether.

Benzoin oxime can be cyanoethylated on both the oximino group and the alcoholic hydroxyl group to yield the mixed ether.⁷⁷



Cyanoethylation of Hydrogen Sulfide, Mercaptans, and Thiophenols (Table IX)

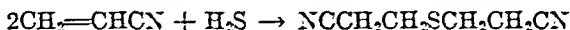
Acrylonitrile reacts with hydrogen sulfide to yield bis-2-cyanoethyl sulfide⁷⁸ when heated in butanol at 80° in an autoclave. The reaction

⁷³ Bachman and Levine, *J. Am. Chem. Soc.*, **69**, 2343 (1947).

⁷⁴ Bruson and Riener, U. S. pat. 2,352,516 [*C.A.*, **38**, 5506 (1944)].

⁷⁵ Keysner, U. S. pat. 2,163,176 [*C.A.*, **33**, 7819 (1939)].

requires no catalyst but is accelerated by alkalies such as sodium hydroxide or Triton B. At atmospheric pressure and at 25° to 75° acrylonitrile



nitrile does not react with hydrogen sulfide in the absence of an alkaline catalyst, but a trace of sodium methoxide or Triton B brings about an exothermic reaction and gives an 86–93% yield of *bis*-2-cyanoethyl sulfide.⁷⁷ The same product is formed when an aqueous solution of sodium sulfide or sodium hydrogen sulfide reacts with acrylonitrile at room temperature.^{78,79}

Aliphatic mercaptans, dimercaptans, and thiophenols add readily to acrylonitrile in the presence of alkaline catalysts. Methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, isobutyl, carbethoxymethyl, benzyl, and dodecyl mercaptans, thiophenol, and *o*-, *m*-, and *p*-thiocresol are reported to react in the presence of strong bases.^{57,80} Piperidine has been used as a catalyst for the reactions involving ethyl mercaptan, benzyl mercaptan, β -mercaptoethanol, and ethylene dithiol.⁸¹ Sodium methoxide is also effective and was employed in the addition of octyl, nonyl, and lauryl mercaptans to acrylonitrile.⁸²



Other, more complex mercaptans which have been studied are 2-mercaptobenzothiazole,^{83,84} 2-mercaptothiazoline, 2-mercapto-4-methylthiazole, and 2-mercaptobenzoxazole.⁵⁷ Hurd and Gershbein⁵⁷ have shown that benzyl, hydroxyethyl, and phenyl mercaptans add to acrylonitrile in the absence of alkalies to give excellent yields of cyanoethylation products. The sulphydryl group in hydroxyethyl mercaptan reacts first. Alkali is required for cyanoethylation of the hydroxyl group. According to one report thiourea and thiocarbanilide add in the mercaptol form to acrylonitrile;⁸⁵ according to another report, however, thiourea and acrylonitrile do not react at 100° in the presence of alkali.⁵⁷

The sodium salts of dialkyldithiocarbamic acids, such as dimethyl- and dibutyl-dithiocarbamic acid and piperidinodithiocarbamic acid, in aqueous solution add to acrylonitrile to yield the corresponding cyano-

⁷⁷ Gershbein and Hurd, *J. Am. Chem. Soc.*, **69**, 242 (1947).

⁷⁸ Brason, unpublished work.

⁷⁹ Hollihan and Moss, *J. Ind. Eng. Chem.*, **39**, 223 (1947).

⁸⁰ Harman, U. S. pat. 2,413,917 [*C.A.*, **41**, 2446 (1947)].

⁸¹ Gribbins, Miller, and O'Leary, U. S. pat. 2,397,960 [*C.A.*, **40**, 3542 (1946)].

⁸² Rapoport, Smith, and Newman, *J. Am. Chem. Soc.*, **69**, 694 (1947).

⁸³ Clifford and Lichty, U. S. pat. 2,407,138 [*C.A.*, **41**, 458 (1947)].

ethylated derivatives.⁸⁰ 2-Diethylaminoethanethiol adds readily to



acrylonitrile without the use of a catalyst.⁸¹



Cyanoethylation of Arsines (Table XIII)

Mann and Cookson⁸⁵ have reported that phenylarsine reacts with acrylonitrile to give phenyl-bis-(2-cyanoethyl)arsine.



The reaction is very vigorous with alkaline catalysts such as traces of potassium hydroxide or sodium methoxide.⁸⁶ Analogous reactions have been described with *p*-aminophenylarsine and with diphenylarsine to give $\text{H}_2\text{NC}_6\text{H}_4\text{As}(\text{CH}_2\text{CH}_2\text{CN})_2$ and $(\text{C}_6\text{H}_5)_2\text{AsCH}_2\text{CH}_2\text{CN}$, respectively.⁸⁶

Cyanoethylation of Inorganic Acids and Hydrogen Cyanide (Table XIII)

Hydrogen chloride, hydrogen bromide, hydrogen cyanide, hypochlorous acid, and sulfurous acid as sodium bisulfite have been added to acrylonitrile. Many of the carboxylic acids such as formic, acetic, and benzoic have failed to add either in the presence or absence of alkaline catalysts.

When hydrogen chloride or hydrogen bromide is passed into acrylonitrile with cooling, the corresponding β -chloropropionitrile or β -bromopropionitrile is formed.^{87,88}

Hydrogen cyanide, however, adds to acrylonitrile only when an alkaline catalyst is present.⁸⁹ In the presence of a small amount of potassium cyanide, acrylonitrile and hydrogen cyanide combine at atmospheric pressure to yield succinonitrile.⁹⁰ If a large amount of water and sodium cyanide react with acrylonitrile at 80°, the product is largely succin-

⁸⁴ Clinton, Suter, Laskowski, Jackman, and Huber, *J. Am. Chem. Soc.*, **67**, 597 (1945).

⁸⁵ Mann and Cookson, *Nature*, **157**, 846 (1946).

⁸⁶ Cookson and Mann, *J. Chem. Soc.*, 1947, 618.

⁸⁷ Moureu and Brown, *Bull. soc. chim. France*, (4) **27**, 903 (1920).

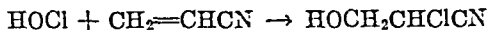
⁸⁸ Stewart and Clark, *J. Am. Chem. Soc.*, **69**, 713 (1947).

⁸⁹ *German Synthetic Fiber Developments*, p. 661, Textile Research Institute, New York, 1946.

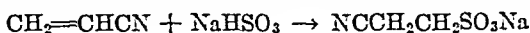
⁹⁰ Kurts, Ger. pat. 707,852 [*C.A.*, **37**, 2747 (1943)].

imide.⁹¹ The addition of hydrogen cyanide in the presence of alkalis to acrylonitrile has been patented by Carpenter.⁹²

Hypochlorous acid does not undergo cyanoethylation. When acrylonitrile is dissolved in water and treated at 0–30° with chlorine or hypochlorous acid, α -chloro- β -hydroxypropionitrile is formed. An excess of calcium carbonate may be added to neutralize any free hydrochloric acid formed.⁹³



Alkali bisulfites in aqueous solution readily add to the α,β -double bond of acrylonitrile to yield alkali metal salts of β -sulfopropionitrile.⁹⁴



Cyanoethylation of Haloforms (Table XIII)

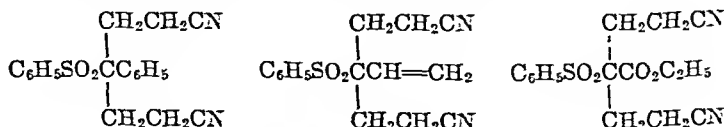
Chloroform⁹⁵ and bromoform⁹⁶ add to acrylonitrile in the presence of Triton B or potassium hydroxide to give γ -trichlorobutyronitrile (11% yield) and γ -tribromobutyronitrile, respectively. Iodoform does



not add to acrylonitrile under the same conditions.

Cyanoethylation of Sulfones (Table XIII)

Mixed aromatic aliphatic sulfones in which the aliphatic carbon atom joined to the sulfur atom is attached to a multiple linkage add to acrylonitrile in the presence of alkaline catalysts.⁹⁶ Such sulfones are illustrated by $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{C}_6\text{H}_5$, $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{CH}=\text{CH}_2$, and $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$. Two molecules of acrylonitrile react.⁹⁷



⁹¹ Wolz, Ger. pat. 741,156 [*C.A.*, 40, 1173 (1946)].

⁹² Carpenter, U. S. pat. 2,434,606 [*C.A.*, 42, 2615 (1948)].

⁹³ Tuerck and Lichtenstein, Brit. pat. 566,006 [*C.A.*, 40, 5772 (1946)].

⁹⁴ Carpenter, U. S. pat. 2,312,878 [*C.A.*, 37, 5199 (1943)].

⁹⁵ Bruson, Niederhauser, Riener, and Hester, *J. Am. Chem. Soc.*, 67, 601 (1945).

⁹⁶ Niederhauser and Bruson, U. S. pat. 2,379,097 [*C.A.*, 39, 4618 (1945)].

⁹⁷ Bruson, U. S. pat. 2,435,552 (1948)].

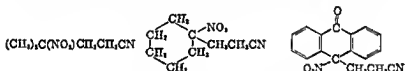
Cyanoethylation of Aliphatic Nitro Compounds (Table XI)

Acrylonitrile reacts with aliphatic nitro compounds having a methinyl, methylene, or methyl group contiguous to the nitro group. The usual alkaline catalysts, potassium hydroxide, sodium ethoxide, or Triton B, are required.^{87, 88, 98, 100}

Nitromethane and acrylonitrile in equimolar quantities with sodium hydroxide as a catalyst react to give primarily the mono-cyanoethylation product, $O_2NCH_2CH_2CH_2CN$.¹⁰¹ With excess acrylonitrile the crystalline *tris*(2-cyanoethyl)nitromethane, $O_2NC(CH_2CH_2CN)_3$, is the chief product, and is accompanied by varying amounts of mono- and di-cyanoethylation derivatives.^{87, 101}

Nitroethane yields a mixture of mono- and di-cyanoethylation products, γ -nitrovaleronitrile, $CH_3CH(NO_2)CH_2CH_2CN$, and γ -nitro- γ -methylpimelonitrile, $CH_3C(NO_2)(CH_2CH_2CN)_2$.^{101, 102} Similarly, 1-nitropropane reacts to give a mixture of $C_2H_5CH(NO_2)CH_2CH_2CN$ and $C_2H_5C(NO_2)(CH_2CH_2CN)_2$.

2-Nitropropane,^{101, 103} nitrocyclohexane,^{88, 99} and 9-nitroanthrone,¹⁰² molecules in which only mono-cyanoethylation is possible, give the expected products, γ -methyl- γ -nitrovaleronitrile, 1-nitro-1-(β -cyanoethyl)cyclohexane, and 9-nitro-9-cyanoethylanthrone, respectively.



Cyanoethylation of Ketones (Table X)

Acrylonitrile reacts with ketones possessing methinyl, methylene, and methyl groups contiguous to the carbonyl group to introduce one, two, three, or more cyanoethyl groups.¹⁰³ The mode of operation and the catalysts are the same as those described for the cyanoethylation of alcohols or amines: the oxides, hydroxides, alkoxides, amides, or hydrides of the alkali metals, the alkali metals themselves, or especially

⁸⁷ I.G. Farbenind. A.-G., Fr. pat. 882,027 (1943).

⁸⁸ Wulff, Hopff, and Wiest, U. S. pat. appl. Ser. No. 404,150 (1943).

⁸⁹ Buckley and Lowe, Brit. pat. 584,050 [C.A., 41, 3478 (1947)].

¹⁰¹ Buckley and Lowe, Brit. pat. 586,099.

¹⁰² Bruson, U. S. pat. 2,361,259 [C.A., 39, 2079 (1945)].

¹⁰³ Bruson and Riener, *J. Am. Chem. Soc.*, 64, 2850 (1942).

Triton B; advantageously in the presence of inert solvents or diluents to control the reaction.



Acetone and acrylonitrile in equimolecular proportions give a small yield of mono-cyanoethylation product, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CN}$.¹⁵⁴ With three moles of acrylonitrile in the presence of sodium hydroxide or Triton B as catalyst, the crystalline tri-cyanoethylation derivative, $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$, is obtained in 75–80% yield,^{153, 155} and upon further cyanoethylation a crystalline tetra addition product can be isolated, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$.

The unsymmetrical aliphatic methyl ketones, such as methyl ethyl ketone,¹⁵⁶ methyl *n*-propyl ketone, methyl isobutyl ketone, methyl *n*-amyl ketone, and methyl *n*-hexyl ketone, react with acrylonitrile in the presence of alkaline catalysts to cyanoethylate the methylene in preference to the methyl group.^{153, 157} The mono-cyanoethylation product, $\text{CH}_3\text{COCH}(\text{R})\text{CH}_2\text{CH}_2\text{CN}$, is not readily obtained in good yield since it is cyanoethylated further; with two moles of acrylonitrile the chief product is $\text{CH}_3\text{COC}(\text{R})(\text{CH}_2\text{CH}_2\text{CN})_2$. Excess of acrylonitrile gives a trisubstitution product, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{COC}(\text{R})(\text{CH}_2\text{CH}_2\text{CN})_2$, in which the methyl group has reacted; higher cyanoethylation derivatives from further reaction of the methyl group have been described.¹⁵³ Methyl isobutyl ketone reacts less readily than methyl *n*-amyl ketone.

Other aliphatic ketones have been studied. Diethyl ketone and excess acrylonitrile give chiefly a tri-cyanoethylation product,¹⁵³ $\text{CH}_3\text{C}(\text{CH}_2\text{CH}_2\text{CN})_2\text{COCH}(\text{CH}_2\text{CH}_2\text{CN})\text{CH}_3$. Diisopropyl ketone reacts sluggishly, probably owing to steric hindrance, but the mono- and the di-substitution products, $(\text{CH}_3)_2\text{C}(\text{CH}_2\text{CH}_2\text{CN})\text{COCH}(\text{CH}_3)_2$ and $(\text{CH}_3)_2\text{C}(\text{CH}_2\text{CH}_2\text{CN})\text{COC}(\text{CH}_2\text{CH}_2\text{CN})(\text{CH}_3)_2$, have been isolated.¹⁵⁷ Diisobutyl ketone does not react appreciably with acrylonitrile. Dibenzyl ketone and acrylonitrile combine to give a resinous mixture from which the tribasic acid, $\text{C}_6\text{H}_5\text{C}(\text{CH}_2\text{CH}_2\text{CO}_2\text{H})_2\text{COCH}(\text{CH}_2\text{CH}_2\text{CO}_2\text{H})\text{C}_6\text{H}_5$, has been isolated after alkaline hydrolysis.¹⁵³ Phenylacetone yields the di-cyanoethylated product, γ -acetyl- γ -phenylpimelonitrile, $\text{C}_6\text{H}_5\text{C}(\text{CH}_2\text{CH}_2\text{CN})_2\text{COCH}_3$, in 86% yield.¹⁵³

Alicyclic ketones react like their aliphatic analogs but more readily. Cyclopentanone¹⁵³ and cyclohexanone¹⁵⁸ and its 4-substituted derivatives¹⁵³ react with four moles of acrylonitrile to give products with all

¹⁵⁴ Shannon, U. S. pat. 2,351,371 [C.A., 40, 350 (1945)].

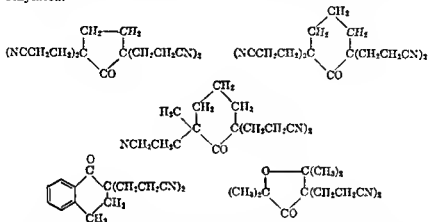
¹⁵⁵ Bruson, U. S. pat. 2,311,153 [C.A. 37, 4509 (1943)].

¹⁵⁶ Wiest and Glaser, U. S. pat. 2,403,570 [C.A., 40, 649S (1946)].

¹⁵⁷ Bruson, U. S. pat. 2,386,736 [C.A., 40, 7234 (1946)].

¹⁵⁸ Bruson, U. S. pat. 2,287,510 [C.A., 37, 149 (1943)].

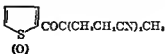
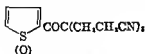
the hydrogens on the two carbon atoms adjacent to the carbonyl group replaced. The mono- and di-cyanoethylated products have been isolated, but poly-cyanoethylation takes place very readily and even with limited amounts of acrylonitrile the tetra addition product is formed. 2-Methylcyclohexanone is tri-cyanoethylated while α -tetralone¹⁰⁸ and 2,2,5,5-tetramethyltetrahydrofuran-3-one are di-cyanoethylated.



Aromatic aliphatic ketones react very readily. The methyl ketones, exemplified by acetophenone and its homologs, *p*-methyl, *p*-methoxy-, *p*-chloro-, *p*-bromo-, and *p*-phenyl-acetophenone, give crystalline tri-cyanoethylation products, $\text{ArCOC}(\text{CH}_2\text{CH}_2\text{CN})_3$, in good yields.¹⁰⁸ The addition products with one and two molecules of acrylonitrile are not described. 2-Naphthyl methyl ketone reacts similarly.¹⁰⁸ Even acetomesitylene, which frequently enters into reaction in its enol form, gives a 30% yield of the tri-cyanoethylation product.¹⁰⁸

Propiophenone and desoxybenzoin represent molecules with only two hydrogens on the carbon attached to the carbonyl group and thus di-cyanoethylation derivatives result, γ -benzoyl- γ -methylpimelonitrile, $\text{C}_6\text{H}_5\text{COC}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})_2$, and $\text{C}_6\text{H}_5\text{COC}(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$.

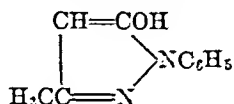
Heterocyclic alkyl ketones are equally reactive. 2-Thienyl methyl ketone and 2-furyl methyl ketone yield crystalline tri-cyanoethylation products,^{34, 109} and 2-thienyl ethyl ketone and 2-furyl ethyl ketone yield di-cyanoethylation products.³⁴



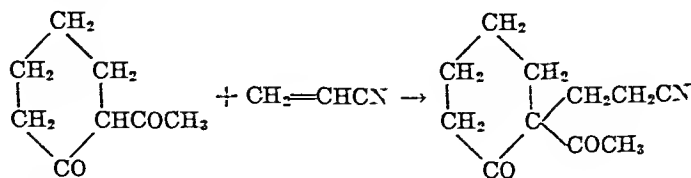
¹⁰⁸ Bruson, U. S. pat. 2,394,962 [C.A., 40, 2848 (1946)].

The methylene group in β -keto esters and their derivatives reacts with acrylonitrile in the presence of alkaline catalysts.^{103, 107, 109, 110} Thus methyl or ethyl acetoacetate and the anilide, *o*-chloroanilide, and 2,5-dichloroanilide¹⁰⁷ give di-cyanoethylation products, $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{CO}_2\text{R}$ and $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{CONHAr}$.

Several 1,3-diketones which have been studied have failed to react with acrylonitrile; among these are 1,3-cyclohexanedione and methylenebis-dihydroresoreinol.²² The explanation offered is that the high degree of acidity effectively neutralizes the catalyst. It is essential that the reaction mixture be alkaline to moist litmus for the reaction to occur.²² A similar explanation is given for the non-reactivity with acrylonitrile of 1-phenyl-3-methylpyrazolone, which exists primarily in the enol form.²²



On the other hand, certain 1,3-diketones in which one carbonyl group is part of an alicyclic ring react readily with acrylonitrile in the presence of aqueous potassium hydroxide or Triton B to introduce a cyanoethyl group between the two carbonyl groups.²² 2-Acetylcyclopentanone, 2-acetylcyclohexanone, and 2-acetylcycloheptanone all react similarly. Boese has described the cyanoethylation of certain 2,4-diketones, notably acetylacetone, benzoylacetone, 3-benzylpentane-2,4-dione and 3-ethylpentane-2,4-dione.^{111, 112}



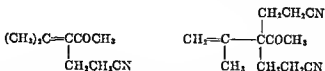
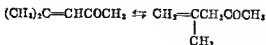
Mesityl oxide, an α,β -unsaturated ketone, reacts with two moles of acrylonitrile in the presence of Triton B to give a 73% yield of a crystalline di- and a 10% yield of a liquid mono-cyanoethylation product. The latter upon further treatment with acrylonitrile is converted to the former. The structures of both products have been established,²³ the mono- as a derivative of the α,β -unsaturated form and the di- as a derivative of the β,γ -desmotrope. The mono-cyanoethylation product

¹⁰³ Wiest and Glaser, U. S. pat. 2,396,626 [C.A., 40, 3771 (1946)].

¹¹¹ Boese, U. S. pat. 2,438,961 (1948).

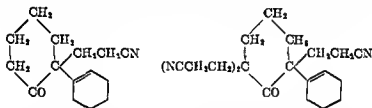
¹¹² Boese, U. S. pat. 2,438,594 (1948).

may result from an initial reaction with the desmotropic form followed



by rearrangement to the α,β -unsaturated ketone.

The β,γ -unsaturated ketone, 2-cyclohexenylcyclohexanone, adds to acrylonitrile to yield a crystalline mono-cyanoethylation product in which the hydrogen of the methinyl group has reacted. Further cyanoethylation then occurs on the methylene group adjacent to the carbonyl.²³



Acrylonitrile reacts with polyketones to cyanoethylate the methylene groups adjacent to the carbonyl groups. Polymeric ketones obtained from carbon monoxide and olefins, the polymers of methyl vinyl ketone and of methyl isopropenyl ketone, and copolymers of alkyl vinyl ketones with olefins and diolefins have been used in this reaction.²²

Cyanoethylation of Aldehydes (Table X)

Acrylonitrile reacts in the presence of alkaline catalysts with those aldehydes in which the α -carbon atom has one or more hydrogen atoms.

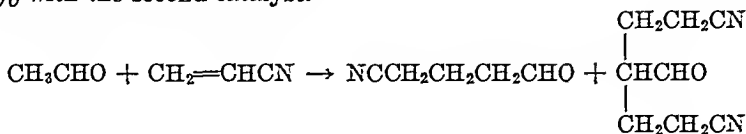
Formaldehyde reacts as methylene glycol with acrylonitrile and yields derivatives which were discussed under alcohols (p. 93).

Acetaldehyde aldolizes and resinifies readily in the presence of alkalis and therefore yields a mixture of cyanoethylation products.²⁴ With concentrated aqueous sodium hydroxide or with sodium cyanide as catalyst, a mixture of γ -cyanobutyraldehyde and γ -formylpimelonitrile

²² Mortenson, U. S. pat. 2,396,963 [C.A., 40, 3937 (1946)].

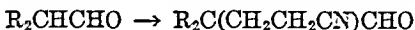
²⁴ Bruson and Ruener, U. S. pat. 2,353,687 [C.A., 38, 6432 (1944)].

is produced in combined yield of 40-50% with the first catalyst and 38% with the second catalyst.^{115, 116}

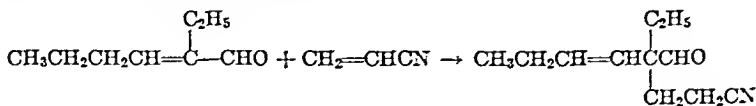


Propionaldehyde and acrylonitrile give α -methyl- γ -cyanobutyraldehyde and γ -methyl- γ -formylpimelonitrile in 5% and 25% yields, respectively.^{115, 116}

Dialkylacetaldehydes, such as isobutyraldehyde, diethylacetaldehyde, and 2-ethylhexanal, are more stable to alkaline reagents and undergo cyanoethylation readily. Isobutyraldehyde and acrylonitrile with saturated aqueous sodium hydroxide as catalyst at 65-80° give a 35-40% yield of α, α -dimethyl- γ -cyano-*n*-butyraldehyde, $(\text{CH}_3)_2\text{C}(\text{CH}_2\text{CH}_2\text{CN})\text{-CHO}$.¹¹⁶ It is reported that the same product is obtained by use of 20% aqueous potassium cyanide as catalyst at a temperature of 80-90°.¹¹⁷ In the other dialkylacetaldehydes in which each of the alkyl groups has at least two carbons, the yields of cyanoethylation products with 50% aqueous potassium hydroxide as catalyst are about 80%.¹¹⁸



α -Ethyl- β -propylacrolein and acrylonitrile in equimolar quantities in the presence of concentrated aqueous or methanolic potassium hydroxide react, even though an α -hydrogen is lacking in the aldehyde, to give a 50% yield of product. Apparently a hydrogen atom and the double bond undergo a shift which permits the introduction of a cyanoethyl group in the rearranged product.¹¹⁴



The behavior of acrylonitrile with benzaldehyde in the presence of alkaline catalysts has not been explained. Two products are formed: one a liquid, b.p. 225-230°/5 mm., consisting of one molecule of benzaldehyde and two of acrylonitrile; and the other a colorless solid, m.p. 73°, b.p. 270°/3 mm.¹¹⁴

¹¹⁵ E. I. du Pont de Nemours & Co., Brit. pat. 576,427 (1946).

¹¹⁶ Walker, U. S. pat. 2,403,086 [C.A., 41, 1235 (1947)].

¹¹⁷ I.G. Farbenind. A.-G., Fr. pat. 886,846 (1943).

¹¹⁸ Bruson and Riener, *J. Am. Chem. Soc.*, 66, 56 (1944).

Cyanoethylation of Derivatives of Malonic and Cyanoacetic Acids (Table XI)

Acrylonitrile and the esters or amides of malonic acid react at 30–50° in the presence of alkaline catalysts, in particular sodium, sodium ethoxide, potassium hydroxide, or Triton B, to form mono- or di-cyanoethylation products.⁹⁷ Monoalkylated malonic esters are mono-cyanoethylated under the same conditions.^{97,119}



From equimolar quantities of acrylonitrile and ethyl malonate with sodium ethoxide as a catalyst, a 40–45% yield of a mono-cyanoethylation product results, $\text{NCCCH}_2\text{CH}_2\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$.¹²⁰ This same product is obtained in small amounts when sodium is used as catalyst, but the di-cyanoethylated malonic ester, γ,γ -dicarbethoxypimelonitrile, is formed chiefly.¹²⁰ An 82.5% yield of this latter compound results from the condensation of two moles of acrylonitrile and one mole of malonic ester in the presence of Triton B; malonamide reacts equally well to give an analogous product.⁹⁷

Of the monoalkylated diethyl malonates, ethyl, *n*-butyl, benzyl,⁹⁷ and cyclopentyl¹¹⁹ have been studied, and they react smoothly with one mole of acrylonitrile, sodium alkoxide or Triton B being used as catalyst. All the products have the formula $\text{RC}(\text{CH}_2\text{CH}_2\text{CN})(\text{CO}_2\text{R})_2$.

Ethyl cyanoacetate and two moles of acrylonitrile give with Triton B essentially a quantitative yield of γ -carbethoxy- γ -cyanopimelonitrile, $\text{C}_2\text{H}_5\text{O}_2\text{CC}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$.⁹⁷ Sodium, sodium hydroxide, and cyclohexylamine have also been used as catalysts in this reaction.¹²⁰ Cyanoacetamide and acrylonitrile with Triton B give a 70% yield of $\text{NCC}(\text{CONH}_2)(\text{CH}_2\text{CH}_2\text{CN})_2$.⁹⁷

Cyanoethylation of Arylacetonitriles (Table XII)

Benzyl cyanide and substituted benzyl cyanides, ArCH_2CN , react vigorously with acrylonitrile if traces of strong bases are present. It is usually difficult to isolate the mono-cyanoethylation products in good yield, but the di-cyanoethylation products are obtained in excellent yields.

¹¹⁹ Lochte, Thomas, and Truitt, *J. Am. Chem. Soc.*, **66**, 551 (1944).

¹²⁰ Koelsch, *J. Am. Chem. Soc.*, **65**, 2458 (1943).

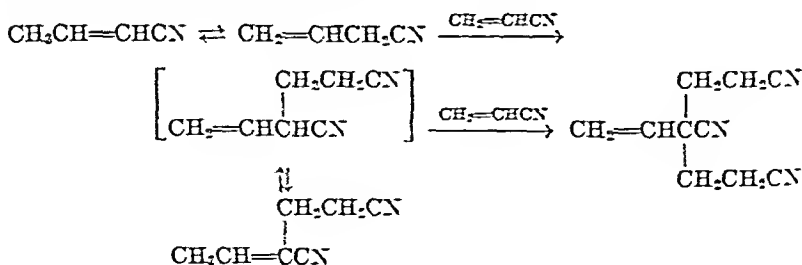
The reaction resembles that which takes place with certain aryl sulfones and related compounds described in the section on sulfones (p. 98).

Benzyl cyanide and acrylonitrile in equimolar proportions with sodium ethoxide as a catalyst give a 20–33% yield of α -phenylglutaronitrile, $C_6H_5CH(CH_2CH_2CN)CN$.¹² A solution of benzyl cyanide in *tert*-butyl alcohol with a little potassium hydroxide as a catalyst rapidly takes up two moles of acrylonitrile to form γ -cyano- γ -phenylpimelonitrile in 94% yield.^{37, 121} With sodium as a catalyst, a 78.5% yield is reported.¹¹⁹

p-Nitrobenzyl cyanide in dioxane solution with Triton B catalyst gives a 91% yield of γ -cyano- γ -(*p*-nitrobenzyl)pimelonitrile.³⁷ *p*-Chlorobenzyl cyanide, *p*-isopropylbenzyl cyanide, and α -naphthylacetonitrile have also been di-cyanoethylated in good yield.¹²²

Cyanoethylation of α,β -Unsaturated Nitriles (Table XII)

Crotononitrile reacts with acrylonitrile in the presence of basic catalysts, in particular Triton B, to give two products, α -ethylidene glutaronitrile and γ -cyano- γ -vinylpimelonitrile.^{23, 123} The same products are obtained from allyl cyanide and acrylonitrile with Triton B. α -Ethylidene-glutaronitrile is converted to γ -cyano- γ -vinylpimelonitrile by means of acrylonitrile and catalyst. The exact mechanism for the formation of these two products is not clear though the presumption is that allyl cyanide, which is desmotropic with crotononitrile, is probably the form which reacts with the acrylonitrile. The sequence of reactions may be formulated in the following way.



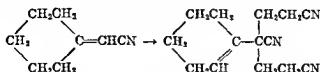
The α,β -unsaturated nitrile represents the stable form after mono-cyanoethylation; the β,γ -unsaturated nitrile is the only possible form for the di-cyanoethylated derivatives.²² The reaction resembles that of mesityl oxide described in the ketone section (p. 102).

¹²¹ Hester and Bruson, U. S. pat. 2,305,529 [C.A., 37, 3205 (1943)].

¹²² Rubin and Wishinsky, *J. Am. Chem. Soc.*, 68, 828 (1946).

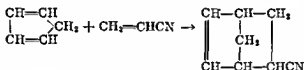
¹²³ Bruson, U. S. pat. 2,352,515 [C.A., 38, 5622 (1944)].

β -Methylcrotononitrile, $(\text{CH}_3)_2\text{C}=\text{CHCN}$, and methallyl cyanide, $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{CN}$, react in a similar manner to yield $(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_2\text{CH}_2\text{CN})\text{CN}$ and $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{CH}_2\text{CH}_2\text{CN})_2\text{CN}$.²³ Another example of a similar rearrangement is that which takes place upon reaction of cyclohexylideneacetonitrile and acrylonitrile to give α,α -di-(2-cyanoethyl)cyclohexenylacetonitrile.^{23, 23a}

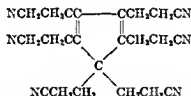


Cyanoethylation of Cyclic Dienes (Table XIII)

Cyclopentadiene reacts with acrylonitrile in the absence of a catalyst to form a 1,4-adduct of the Diels-Alder type.¹²⁴ In the presence of Triton

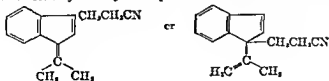


B, however, the Diels-Alder addition is completely repressed and all six hydrogen atoms in cyclopentadiene react to give a crystalline hexacyanoethylation derivative, accompanied by a mixture of lower polycyanoethylation products.¹²⁴



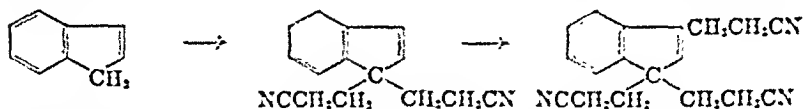
The fulvenes behave in a similar manner.¹²⁴ No Diels-Alder reaction occurs in the presence of Triton B when dimethylfulvene and acrylonitrile react. Only cyanoethylation products are formed.

Acrylonitrile and ω,ω -dimethylbenzofulvene with Triton B yield a crystalline mono-cyanoethylation product whose structure is uncertain.

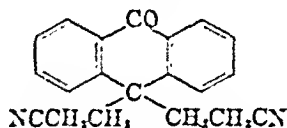
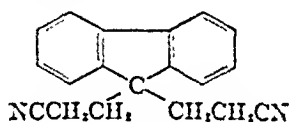


¹²⁴ Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

Indene with acrylonitrile and Triton B as catalyst yields primarily a crystalline *tris*(2-cyanoethyl)indene even when equimolar quantities of reactants are employed. A small amount of di-cyanoethylation product may be isolated. With three mole equivalents of acrylonitrile the yield of primary product is over 90%.¹²⁴ Fluorene and anthrone with acrylo-



nitrile and Triton B give exclusively di-cyanoethylation products in 75–80% yields.^{124,125} The reactions of indene, fluorene, and anthrone



with acrylonitrile take place at room temperature with evolution of heat. In order to prevent excessive polymerization of the acrylonitrile and to allow cyanoethylation to go to completion, the use of inert solvents such as *tert*-butyl alcohol or dioxane, which dissolve the solid methylene compounds and moderate the reaction, is helpful.

EXTENSION OF THE REACTION TO HIGHER HOMOLOGS OF ACRYLONITRILE

Substituted acrylonitriles such as α -methylacrylonitrile and crotononitrile react less readily than acrylonitrile with the various classes of compounds considered in the preceding section of this chapter. It has not been possible to add aldehydes or ketones to α -methylacrylonitrile, although strongly basic amines such as piperidine do add to it.²² Alcohols add to α -methylacrylonitrile, but the yields of alkoxy nitriles resulting are much lower than in the comparable reactions with acrylonitrile.²² Crotononitrile is much more reactive than α -methylacrylonitrile. Alcohols,¹²⁶ amines, and nitroparaffins²² add readily to crotononitrile, and fluorene can be added to it.¹²⁷

β -Vinylacrylonitrile reacts readily with nitroparaffins, malonic ester, and highly enolized ketones such as acetoacetic ester under conditions similar to those used for cyanoethylation to yield addition products

¹²⁵ Bruson, U. S. pat. 2,280,058 [C.A., 36, 5188 (1942)].

¹²⁶ Bruylants, *Bull. soc. chim. Belg.*, 31, 225 (1922 [C.A., 17, 1427 (1923)]).

¹²⁷ Bruson, U. S. pat. 2,301,518 [C.A., 37, 2101 (1943)].

containing the $-\text{CH}_2\text{CH}=\text{CHCH}_2\text{CN}$ group in place of one or more of the reactive hydrogen atoms.¹²³

EXPERIMENTAL CONDITIONS AND PROCEDURES

Acrylonitrile boils at 78° and is soluble in water to the extent of about 7.3% at 20° . Its vapor is toxic, and it should therefore be handled with due caution, preferably in a well-ventilated room or in a hood. Many cyanoethylation reactions are slow in starting and become strongly exothermic rather suddenly. It is advisable therefore to provide a cooling bath of ice water and to add the acrylonitrile dropwise with stirring to the other component advantageously in the presence of an inert solvent. Most cyanoethylation products are soluble in ethylene dichloride, and this solvent can be used to extract them from the reaction mixture or from any polyacrylonitrile that may be formed.

Ethylamine and Acrylonitrile; Preparation of β -Ethylaminopropionitrile and bis(2-Cyanoethyl)ethylamine.² One hundred and six grams (2 moles) of acrylonitrile is added to 200 g. (3 moles) of a 70% aqueous solution of ethylamine over a period of two hours while the temperature is kept below 30° . The reaction mixture is stirred at room temperature for five hours and finally heated on the steam bath for one hour. After the reaction mixture has stood overnight, the water is removed by adding 50 g. of anhydrous potassium carbonate and separating the aqueous layer. Distillation at $92-95^\circ/30$ mm. gives 177 g. (90%) of β -ethylaminopropionitrile.

When 130 g. (2 moles) of 70% ethylamine solution is added to 250 g. (4.7 moles) of acrylonitrile and the warm mixture heated on the steam bath for two hours and worked up as indicated above, 180.5 g. (60%) of bis(2-cyanoethyl)ethylamine, b.p. $202-205^\circ/30$ mm., is obtained.

Carbazole and Acrylonitrile; Preparation of 9-(β -Cyanoethyl)carbazole.¹ An intimate mixture of 167 g. (1.0 mole) of carbazole and 250 ml. (3.8 moles) of acrylonitrile is cooled in an ice bath, and 2 ml. of a 40% solution of benzyltrimethylammonium hydroxide (Triton B) is added to the well-stirred mixture. Upon addition of the catalyst a vigorous reaction ensues; the mixture warms up, and the pasty mass partially solidifies. The mixture is heated on the steam bath for one hour, and upon cooling a mass of crystals separates from the solution. These are removed by filtration and combined with a second crop of crystals obtained by concentrating the mother liquors. The yield is 188 g. (85.4%); m.p. 155.5° .

¹²³ Charlsh, Davies, and Rose, *J. Chem. Soc.*, 1948, 227, 232.

p-Anisidine and Acrylonitrile; Preparation of β -(*p*-Anisidino)propionitrile.²³ Equimolecular quantities of *p*-anisidine and acrylonitrile are refluxed with acetic acid (25 ml. per mole) for twelve hours. The mixture is dissolved in ether, washed successively with water and 5% bicarbonate solution, dried, and distilled. The yield of material boiling at 247°/0.7 mm. is 70%.

Butanol and Acrylonitrile; Preparation of β -*n*-Butoxypropionitrile.⁴⁴ A mixture of 148 g. (2.0 moles) of *n*-butanol and 2 g. of 40% benzyltrimethylammonium hydroxide (Triton B) is stirred under a reflux condenser while 106 g. (2 moles) of acrylonitrile is added at a rate such that the temperature does not exceed 45°. The mixture is stirred an hour after all the acrylonitrile has been added, made acidic with acetic acid, and fractionated in vacuum through a jacketed Vigreux column. The product boils at 98°/20 mm.; yield, 219 g. (86%).

Ethylene Cyanohydrin and Acrylonitrile; Preparation of *bis*-2-Cyanoethyl Ether.³⁷ To a stirred mixture of 710 g. (10 moles) of ethylene cyanohydrin and 25 g. of 20% aqueous potassium hydroxide, 530 g. (10 moles) of acrylonitrile is added dropwise during the course of two and three-quarters hours while the reaction temperature is maintained at 40°. The mixture is stirred for eighteen hours at room temperature. It is then neutralized with dilute hydrochloric acid and evaporated to dryness in vacuum (30 mm.) on a steam bath. The residual oil, which weighs 1197 g., is distilled in vacuum to give 1126 g. (91%) of the product as a colorless liquid boiling at 155–165°/3 mm.

Formaldehyde, *tert*-Butyl Alcohol, and Acrylonitrile; Preparation of *tert*-Butyl 2-Cyanoethyl Formal.⁶⁹ To a rapidly stirred suspension of 30 g. (1.0 mole) of paraformaldehyde, 100 g. of *tert*-butyl alcohol, and 5 g. of 30% methanolic potassium hydroxide, 53 g. (1.0 mole) of acrylonitrile is added dropwise during thirty minutes. The temperature rises spontaneously from 25° to about 45°, and the paraformaldehyde goes into solution. The mixture is stirred and heated for an hour and a half at 35–40° to complete the reaction. It is then filtered to remove a small amount of undissolved paraformaldehyde, and the filtrate is washed several times with water until it is no longer alkaline to litmus. The washed oil is then distilled in vacuum to yield 63 g. (40%) of the formal, $(\text{CH}_3)_3\text{COCH}_2\text{OCH}_2\text{CH}_2\text{CN}$, which boils at 100–102°/10 mm.

β -Naphthol and Acrylonitrile; Preparation of 1-(2-Cyanoethyl)-2-hydroxynaphthalene.⁷¹ A mixture of 55 ml. of benzene, 29 g. (0.2 mole) of β -naphthol, 9 g. of sodium hydroxide pellets, and 12 g. (0.22 mole) of acrylonitrile is heated on a steam bath under a reflux condenser for two hours. Then 100 ml. of cold water is added and the mixture stirred until all the alkali has dissolved. The aqueous layer is separated and

acidified with acetic acid to yield 37 g. (93%) of product which, after recrystallization from ethanol, melts at 142°.

Sodium Sulfide and Acrylonitrile; Preparation of bis-2-Cyanoethyl Sulfide.⁷⁸ To a stirred solution of 480 g. (2.0 moles) of sodium sulfide nonahydrate and 400 g. of water, 212 g. (4.0 moles) of acrylonitrile is added dropwise while cooling to 12–20°. After the addition, which requires about one and one-quarter hours, the mixture is stirred at room temperature for four hours. The product usually crystallizes, especially if seeded and cooled. If it does not crystallize, the oil is taken up in benzene, washed with water, and dried in vacuum at 95°. The 247 g. of residual oil upon distillation in vacuum yields 240 g. (86%) of product boiling at 160–170°/0.5–1 mm. which crystallizes on cooling.

Hydrogen Cyanide and Acrylonitrile; Preparation of Succinonitrile.⁸⁰ A mixture of 300 g. (5.7 moles) of acrylonitrile and 3 g. of potassium cyanide is stirred under a good reflux condenser with 50 g. (1.9 moles) of liquid hydrogen cyanide. After the mixture has been warmed to 35° for a short time the reaction becomes exothermic and is held at 55–60° by cooling. When the reaction slows down, 105 g. (3.9 moles) of hydrogen cyanide is added dropwise. The reaction is completed by warming for two hours at 60–70°. The product is distilled directly in vacuum to give 424 g. (93%) of succinonitrile, b p. 158–160°/20 mm.

Benzyl Phenyl Sulfone and Acrylonitrile; Preparation of 3-(3-Phenyl-1,5-dicyano)amyl Phenyl Sulfone.⁸¹ To a stirred solution of 5.8 g. (0.025 mole) of benzyl phenyl sulfone, $C_6H_5CH_2SO_2C_6H_5$, 40 g. of acetonitrile, and 0.5 g. of Triton B at 32–38°, there is added 2.7 g. (0.05 mole) of acrylonitrile. The mixture is then stirred for eighteen hours at room temperature and neutralized with dilute hydrochloric acid. The product is washed with water and dried in vacuum at 95°. The 5 g. of residual oil crystallizes when mixed with ethanol and, after two recrystallizations from ethanol, forms colorless crystals, m.p. 180° (yield 55%).

Acetone and Acrylonitrile; Preparation of 1,1,1-tris(2-Cyanoethyl)-acetone.¹⁰³ To a stirred solution of 29 g. (0.5 mole) of acetone, 30 g. of *tert*-butyl alcohol, and 2.5 g. of 30% ethanolic potassium hydroxide solution cooled to 0–5°, a solution of 80 g. (1.5 moles) of acrylonitrile and 37 g. of *tert*-butyl alcohol is added dropwise during the course of one and a half hours while the reaction temperature is maintained at 0–5°. The mixture is then stirred for two hours at 5°, and the crystalline product is filtered with suction. The yield is 84 g. (79.5%), and the product melts at 154° after crystallization from hot water. *

Methyl Acetoacetate and Acrylonitrile; Preparation of Methyl α,α -Di(2-cyanoethyl)acetoacetate.¹⁰³ To a solution of 58 g. (0.5 mole) of

methyl acetoacetate, 100 g. of dioxane, and 7 g. of Triton B there is gradually added 53 g. (1.0 mole) of acrylonitrile at 30–40°. After stirring for one to three hours the crystalline product is filtered. The yield is 55 g. (50%), and the product melts at 154° after crystallization from acetone.

2-Ethylbutyraldehyde and Acrylonitrile; Preparation of 2-(2-Cyanoethyl)-2-ethylbutyraldehyde.¹¹⁴ To a stirred solution of 700 g. (7 moles) of freshly distilled 2-ethylbutyraldehyde and 20 g. of 50% aqueous potassium hydroxide solution, 408 g. (7.7 moles) of acrylonitrile is added dropwise during two hours at 55–58°. The mixture is stirred for ninety minutes longer, until the exothermic reaction has ceased, and finally is heated for one hour at 55° to complete the reaction. The product is acidified to congo red with dilute hydrochloric acid, washed twice with water, and dried under reduced pressure at 90°; the 1018 g. of residual oil is distilled in vacuum in a current of nitrogen. The product distills at 115–125°/4–6 mm. as a colorless oil. The yield is 821 g. (76.6%).

Ethyl Malonate and Acrylonitrile; Preparation of γ,γ -Dicarbethoxypimelonitrile.³⁷ To a stirred solution of 80 g. (0.5 mole) of ethyl malonate, 100 g. of dioxane, and 10 g. of Triton B, 53 g. (1 mole) of acrylonitrile is added dropwise during forty minutes while the reaction mixture is being cooled to 30–35°. The mixture is stirred for two hours at room temperature; then it is neutralized with dilute hydrochloric acid and poured into 1 l. of ice water. The product separates as an oil which rapidly solidifies to a white crystalline mass. The yield is 110 g. (82.7%), and the melting point is 62° after crystallization from ethanol.

Benzyl Cyanide and Acrylonitrile; Preparation of γ -Cyano- γ -phenylpimelonitrile.³⁷ A solution of 10.6 g. (0.2 mole) of acrylonitrile in 10 g. of *tert*-butyl alcohol is added dropwise to a stirred solution of 11.7 g. (0.1 mole) of benzyl cyanide, 25 g. of *tert*-butyl alcohol, and 1 g. of 30% of methanolic potassium hydroxide solution at 10–25°. The mixture is stirred for two hours at 10–25°, then neutralized with dilute hydrochloric acid and diluted with 25 ml. of ethanol to aid filtration of the crystalline product. The yield is 21 g. (94%). The melting point is 70° after crystallization from ethanol.

Fluorene and Acrylonitrile; Preparation of *bis*-9,9-(2-Cyanoethyl)-fluorene.¹²⁴ During one hour, 111.3 g. (2.1 moles) of acrylonitrile is added dropwise to a rapidly stirred solution of 166 g. (1.0 mole) of fluorene, 500 g. of dioxane, and 5 g. of Triton B, while the reaction temperature is maintained at 30–40° by occasional cooling with ice water. The solution is then stirred for three to six hours at room temperature to complete the reaction. At the end of this time, the dark brown solution is neutralized with dilute hydrochloric acid, and, without interruption of the stirring, 800 ml. of water is added to precipitate the

product in granular form. The filtered and air-dried product weighs 250 g. Upon recrystallization from 500 ml. of ethanol, the product separates as faintly yellow crystals, m.p. 118–119°. The yield is 201 g. (74%). One more recrystallization from ethanol, using Norit, gives the pure compound as white needles, m.p. 121°.

TABLES OF CYANOETHYLATION REACTIONS

The following tables include the examples of cyanoethylation reactions described in the literature covered by *Chemical Abstracts* through 1947. A few articles that appeared in 1948 have been included. Attention is called to the fact that patents sometimes contain reports of cyanoethylation reactions but do not give the properties of the products. Products whose physical properties have not been reported are not included in the tables.

TABLE I

CYANOETHYLATION OF AMMONIA

| Ratio of Moles of Ammonia to Moles of Acrylonitrile | Temp. °C. | Time Hr. | Yields of Products | | | Refer- ence |
|--|--------------|-------------|---|---|--|----------------|
| | | | $\text{H}_2\text{NC}_2\text{H}_4\text{CN}$ % | $\text{HN}(\text{C}_2\text{H}_4\text{CN})_2$ % | $\text{N}(\text{C}_2\text{H}_4\text{CN})_3$ % | |
| 20 * | 30–33 | 24 | 39 | 39 | — | 5 |
| 15 * | 30–33 | 24 | 30 | 40 | — | 5 |
| 10 * | 30–33 | 24 | 35.6 | 53 | — | 5 |
| 7.5 * | 30–33 | 24 | 32.6 | 34.5 | — | 5 |
| 5 * | 30–33 | 24 | 23 | 59.6 | — | 5 |
| 2 * | 30–33 | 24 | 9 | 67.6 | — | 5 |
| 1 * | 30–33 | 3 | — | 63 | — | 32 |
| 0.55 * | 30–33 | 24 | 0 | 87.2 | — | 5 |
| 0.5 * | 30–33 | 24 | 0 | 85 | — | 5 |
| 0.53 * | 30 | — | 1.7 | 83.5 | 6.0 | 3 |
| 0.56 * | 30 | — | 5.8 | 83.5 | 1.0 | 3 |
| 5.9 * | 30 | — | 23.9 | 58.9 | 3.3 | 3 |
| 7.5 † | 30–33 | 24 | 30 | 57 | — | 5 |
| 5 † | 30–33 | 24 | 19 | — | — | 5 |
| 7.5 ‡ | 30–33 | 24 | 20 | 60 | — | 5 |
| 1.25 ‡ | 90 | 0.5 | 12.5 | 75 | — | 1 |
| 8 ‡ | 40 | — | 22 | 64 | — | 2 |
| 7.5 ‡ | — | 24 | 39.3 | 53.2 | — | 5 |
| 5 ‡ | — | 24 | 34.4 | 58.5 | — | 5 |
| 4 ‡ | — | 24 | 35.5 | 57.8 | — | 5 |
| 3 ‡ | — | 24 | 33.2 | 61 | — | 5 |
| 2 ‡ | — | 24 | 24.6 | 68.6 | — | 5 |
| 3–10 * | 110 | 2–5 min. | 60–80 | 15 | — | 4 |

* 28–30% aqueous NH_3 .

† 22% aqueous NH_3 .

‡ 40% aqueous NH_3 .

§ Liquid NH_3 in sealed tube.

|| 28–30% aqueous NH_3 under pressure and no cooling

TABLE II
CYANOMETHYLATION OF PRIMARY AMINES

| Amine | Ratio of Moles of Amine to Moles of Acrylonitrile | Temp. °C. | Time hr. | Product | Yield % | Refer- ence |
|-------------------------------|--|--------------|-------------|--|------------|----------------|
| Hydrazine * | 1 | Cooling | — | $\text{H}_2\text{NNHICH}_2\text{CH}_2\text{CN}$ | 90 | 1 |
| Hydroxylamine hydrochloride † | 0.7 | 30 | 2 | $\text{HONHICH}_2\text{CH}_2\text{CN}$ | 100 | 1 |
| Methylamine ‡ | 1.2 | Cooling | 24 | $\text{CH}_3\text{NHICH}_2\text{CH}_2\text{CN}$ | 78 | 9 |
| Methylamine § | 1.1 | 80 | 6 | $\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 9 |
| Methylamine * | 1.5 | <30 | 24 | $\text{CH}_3\text{NHICH}_2\text{CH}_2\text{CN}$ | 71 | 10 |
| Ethylamine § | 1.5 | Cooling | 5 | $\text{C}_2\text{H}_5\text{NHICH}_2\text{CH}_2\text{CN}$ | 90.4 | 2 |
| Ethylamine § | 0.42 | Boiling | 2 | $\text{C}_2\text{H}_5\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 60 | 2 |
| Ethylamine * | 1.5 | <30 | 24 | $\text{C}_2\text{H}_5\text{NHICH}_2\text{CH}_2\text{CN}$ | 84 | 10 |
| n-Propylamine | 1.5 | <30 | 5 | $n\text{-C}_3\text{H}_7\text{NHICH}_2\text{CH}_2\text{CN}$ | 92 | 10 |
| Isopropylamine | 1.5 | <30 | 24 | $\text{iso-C}_3\text{H}_7\text{NHICH}_2\text{CH}_2\text{CN}$ | 95 | 11 |
| n-Butylamine | 1 | 10-30 | 1 | $n\text{-C}_4\text{H}_9\text{NHICH}_2\text{CH}_2\text{CN}$ | 100 | 1 |
| n-Butylamine | 1.5 | <30 | 5 | $n\text{-C}_4\text{H}_9\text{NHICH}_2\text{CH}_2\text{CN}$ | 98 | 10 |
| sec-Butylamine | 1.5 | <30 | 5 | $\text{sec-C}_4\text{H}_9\text{NHICH}_2\text{CH}_2\text{CN}$ | 83 | 10 |
| tert-Butylamine | 1.5 | <30 | 5 | $\text{tert-C}_4\text{H}_9\text{NHICH}_2\text{CH}_2\text{CN}$ | 50 | 10 |
| n-Amylamine | 1 | 50 | — | $n\text{-C}_5\text{H}_{11}\text{NHICH}_2\text{CH}_2\text{CN}$ | 88 | 14 |
| Cyclohexylamine | 1 | Reflux | 1 | $\text{C}_6\text{H}_{11}\text{NHICH}_2\text{CH}_2\text{CN}$ | 80 | 1 |
| Cyclohexylamine | 1.5 | <30 | 5 | $\text{C}_6\text{H}_{11}\text{NHICH}_2\text{CH}_2\text{CN}$ | 92 | 10 |
| Benzylamine | 1 | — | — | $\text{C}_6\text{H}_5\text{CH}_2\text{NHICH}_2\text{CH}_2\text{CN}$ | 73 | 15 |
| p-Anisidine ¶ | 1 | Reflux | 12 | $\text{CH}_3\text{OC}_6\text{H}_4\text{NHICH}_2\text{CH}_2\text{CN}$ | 70 | 23 |

| | | | | | | |
|---|-----|---------|------|---|------|----|
| Ethanolamine | — | — | — | $\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 2 |
| Ethanolamine | 1 | Cooling | — | $\text{HOCH}_2\text{CH}_2\text{NHCCH}_2\text{CH}_2\text{CN}$ | 100 | 19 |
| γ -Diethylaminopropylamine | 1 | 50 | 21** | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NHCCH}_2\text{CH}_2\text{CN}$ | 79.4 | 2 |
| γ -Diethylaminopropylamine | — | — | — | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 8.8 | 2 |
| Morpholinocethylamine | — | — | — | $\text{OC}_4\text{H}_8\text{NCH}_2\text{CH}_2\text{NHCCH}_2\text{CH}_2\text{CN}$ | 81.5 | 2 |
| Morpholinopropylamine | — | — | — | $\text{OC}_4\text{H}_8\text{NCH}_2\text{CH}_2\text{CH}_2\text{NHCCH}_2\text{CH}_2\text{CN}$ | 76 | 2 |
| 8-(3-Aminopropylamino)-8-methoxyquinoline | 1 | 25 | 6 | 8-[3-(2'-Cyanoethylamino)-propylamino]-8-methoxyquinoline | — | 21 |
| 1-Naphthylamine † | 0.5 | 160 | 16 | N-(β -Cyanoethyl)-1-naphthylamine | — | 22 |

* In aqueous solution.

† In methanol.

‡ In sealed tube.

§ A 70% aqueous solution.

|| With later heating on the steam bath.

¶ In glacial acetic acid as catalyst.

** Allowed to stand forty-eight hours at room temperature after heating.

TABLE III
CYANOETHYLATION OF SECONDARY AMINES

| Amine | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|------------------------------|--------------|-------------|---|------------|-----------|
| Diethyl- | 50 | 24 * | (C ₂ H ₅) ₂ NCH ₂ CH ₂ CN | 97 | 2 |
| Diethyl- | Reflux | 8 † | (C ₂ H ₅) ₂ NCH ₂ CH ₂ CN | 74 | 2 |
| Diethyl- | Reflux | 0.5 † | (C ₂ H ₅) ₂ NCH ₂ CH ₂ CN | 93 | 2 |
| Diethanol- | 60 | — | (HOCH ₂ CH ₂) ₂ NCH ₂ CH ₂ CN | 100 | 19 |
| Diethanol- | 30 | 8 | (HOCH ₂ CH ₂) ₂ NCH ₂ CH ₂ CN | 94 | 2 |
| N-ethyl-ethanol- | 50 | 24 | (C ₂ H ₅)(HOCH ₂ CH ₂)NCH ₂ CH ₂ CN | 72 | 14 |
| Methyl-n-propyl- | 95 | 24 | (CH ₃)(n-C ₃ H ₇)NCH ₂ CH ₂ CN | 93 | 16 |
| Methylisopropyl- § | 95 | 24 | (CH ₃)(iso-C ₃ H ₇)NCH ₂ CH ₂ CN | 76 | 16 |
| Methylisobutyl- § | 95 | 24 | (CH ₃)(iso-C ₄ H ₉)NCH ₂ CH ₂ CN | 78 | 16 |
| Methyl-n-butyl- § | 95 | 24 | (CH ₃)(n-C ₄ H ₉)NCH ₂ CH ₂ CN | 83 | 16 |
| Methyl-sec-butyl- § | 95 | 24 | (CH ₃)(sec-C ₄ H ₉)NCH ₂ CH ₂ CN | 87 | 16 |
| Ethylisopropyl- | 95 | 24 | (C ₂ H ₅)(iso-C ₃ H ₇)NCH ₂ CH ₂ CN | 31 | 16 |
| Isopropyl-n-propyl- § | 95 | 24 | (n-C ₃ H ₇)(iso-C ₃ H ₇)NCH ₂ CH ₂ CN | 80 | 16 |
| Di-n-propyl- | 50 | 24 * | (n-C ₃ H ₇) ₂ NCH ₂ CH ₂ CN | 88 | 2, 14 |
| Dil-isopropyl- | 50 | 24 * | (iso-C ₃ H ₇) ₂ NCH ₂ CH ₂ CN | 12 | 14 |
| Methyl-2-pentyl- § | 95 | 24 | (CH ₃)(C ₅ H ₁₁)NCH ₂ CH ₂ CN | 89 | 16 |
| Methyl-3-pentyl- § | 95 | 24 | (CH ₃)(C ₅ H ₁₁)NCH ₂ CH ₂ CN | 81 | 16 |
| Ethyl-4-isobutyl- § | 95 | 24 | (C ₂ H ₅)(iso-C ₄ H ₉)NCH ₂ CH ₂ CN | 56 | 16 |
| Methyl-2-(2-methylbutyl)- § | 95 | 24 | (CH ₃)(C ₆ H ₁₃)NCH ₂ CH ₂ CN | 66 | 16 |
| Methyl-1-(2-methylpentyl)- § | 95 | 24 | (CH ₃)(C ₆ H ₁₃)NCH ₂ CH ₂ CN | 92 | 16 |
| n-Butyl-n-propyl- § | 95 | 24 | (C ₄ H ₉)(C ₃ H ₇)NCH ₂ CH ₂ CN | 61 | 16 |

| | | | | |
|--------------------------------------|--------|---|------|-------|
| <i>sec</i> -Butyl- <i>n</i> -propyl- | 24 | (<i>sec</i> -C ₄ H ₉)(C ₃ H ₇)NCH ₂ CH ₂ CN | 34 | 16 |
| Isobutyl- <i>n</i> -propyl-† | 24 | (<i>iso</i> -C ₄ H ₉)(C ₃ H ₇)NCH ₂ CH ₂ CN | 40 | 16 |
| 4-Heptyl-methyl-‡ | 24 | (C ₇ H ₁₅)(CH ₃)NCH ₂ CH ₂ CN | 65 | 16 |
| Di- <i>n</i> -butyl- | — | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 64 | 1 |
| | 24* | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 91 | 2 |
| | 21* | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 96 | 2 |
| | 24* | (<i>iso</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 51 | 14 |
| Diisobutyl- | 24 | (<i>n</i> -C ₄ H ₉)(<i>sec</i> -C ₄ H ₉)NCH ₂ CH ₂ CN | 42 | 16 |
| <i>n</i> -Butyl- <i>sec</i> -butyl- | 24 | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 90 | 2, 13 |
| Di- <i>n</i> -amyl- | 24* | (<i>n</i> -C ₅ H ₁₁) ₂ NCH ₂ CH ₂ CN | 85 | 2 |
| Di- <i>n</i> -hexyl- | 100* | (<i>n</i> -C ₆ H ₁₃) ₂ NCH ₂ CH ₂ CN | 80 | 14 |
| Di- <i>n</i> -octyl- | 100* | (C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CN | 65 | 14 |
| Di-2-ethylhexyl- | — | (C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CN | 77 | 2 |
| Di-2-ethylhexyl- | 100 | (C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CH ₂ CH ₂ NCH ₂ CH ₂ CN | 78 | 2 |
| Di-(γ-dithiolaminopropyl)- | 50 | (C ₄ H ₉) ₂ NCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CN | 79.4 | 2 |
| γ-Dithiolaminopropyl- | — | C ₄ H ₉ CH ₂ N(CH ₃)CH ₂ CH ₂ CN | 93 | 15 |
| Benzyl-methyl- | 95 | (C ₆ H ₅)(CH ₃)NCH ₂ CH ₂ CN | 90 | 16 |
| Cyclopentyl-methyl-§ | 95 | (C ₅ H ₉)(CH ₃)NCH ₂ CH ₂ CN | 61 | 16 |
| Cyclohexyl-methyl-§ | 95 | (C ₆ H ₁₁)(C ₃ H ₇)NCH ₂ CH ₂ CN | 48 | 16 |
| Cyclopentyl-ethyl- | 95 | (C ₅ H ₉)(<i>n</i> -C ₄ H ₉)NCH ₂ CH ₂ CN | 68 | 16 |
| Cyclopentyl- <i>n</i> -butyl-§ | 180 | C ₄ H ₉ N(CH ₃)CH ₂ CH ₂ CN | 25 | 2 |
| N-Methylanilino ¶ | Reflux | C ₆ H ₅ N(CH ₃)CH ₂ CH ₂ CN | Good | 22 |
| N-Methylanilino ** | | | | |

* Allowed to stand forty-eight hours at room temperature after heating.

† Distilled immediately after heating.

‡ Allowed to stand in refrigerator twenty-four hours after refluxing.

§ With benzyltrimethyl ammonium hydrosulfate catalyst (Tytol B).

|| With traces of Cu bronze.

¶ Hydrated copper sulfate catalyst

** In glacial acetic acid as catalyst.

TABLE III
CYANOETHYLATION OF SECONDARY AMINES

| Amine | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|--------------------------------------|--------------|-------------|-------------------------------------|------------|-----------|
| Diethyl- | 50 | 24 * | $(C_2H_5)_2NCH_2CH_2CN$ | 97 | 2 |
| Diethyl- | Reflux | 8 † | $(C_2H_5)_2NCH_2CH_2CN$ | 74 | 2 |
| Diethyl- | Reflux | 0.5 † | $(C_2H_5)_2NCH_2CH_2CN$ | 93 | 2 |
| Diethanol- | 60 | — | $(HOCH_2CH_2)_2NCH_2CH_2CN$ | 100 | 19 |
| Diethanol- | 30 | 8 | $(HOCH_2CH_2)_2NCH_2CH_2CN$ | 94 | 2 |
| N-Ethyl-ethanol- | 50 | 24 | $(C_2H_5)(HOCH_2CH_2)NCH_2CH_2CN$ | 72 | 14 |
| Methyl- <i>n</i> -propyl- | 95 | 24 | $(CH_3)(n-C_3H_7)NCH_2CH_2CN$ | 93 | 16 |
| Methylisopropyl- § | 95 | 24 | $(CH_3)(iso-C_3H_7)NCH_2CH_2CN$ | 76 | 16 |
| Methylisobutyl- § | 95 | 24 | $(CH_3)(iso-C_4H_9)NCH_2CH_2CN$ | 78 | 16 |
| Methyl- <i>n</i> -butyl- § | 95 | 24 | $(CH_3)(n-C_4H_9)NCH_2CH_2CN$ | 83 | 16 |
| Methyl- <i>sec</i> -butyl- § | 95 | 24 | $(CH_3)(sec-C_4H_9)NCH_2CH_2CN$ | 87 | 16 |
| Ethylisopropyl- | 95 | 24 | $(C_2H_5)(iso-C_3H_7)NCH_2CH_2CN$ | 31 | 16 |
| Isopropyl- <i>n</i> -propyl- § | 95 | 24 | $(n-C_3H_7)(iso-C_3H_7)NCH_2CH_2CN$ | 80 | 16 |
| Di- <i>n</i> -propyl- | 50 | 24 * | $(n-C_3H_7)_2NCH_2CH_2CN$ | 88 | 2, 14 |
| Diisopropyl- | 50 | 24 * | $(iso-C_3H_7)_2NCH_2CH_2CN$ | 12 | 14 |
| Methyl-2-pentyl- § | 95 | 24 | $(CH_3)(C_5H_{11})NCH_2CH_2CN$ | 89 | 16 |
| Methyl-3-pentyl- § | 95 | 24 | $(CH_3)(C_5H_{11})NCH_2CH_2CN$ | 81 | 16 |
| Ethyl-isobutyl- § | 95 | 24 | $(C_2H_5)(iso-C_4H_9)NCH_2CH_2CN$ | 56 | 16 |
| Methyl-2-(3-methylbutyl)- § | 95 | 24 | $(CH_3)(C_6H_{13})NCH_2CH_2CN$ | 66 | 16 |
| Methyl-4-(2-methylpentyl)- § | 95 | 24 | $(CH_3)(C_6H_{13})NCH_2CH_2CN$ | 92 | 16 |
| <i>n</i> -Butyl- <i>n</i> -propyl- § | 95 | 24 | $(C_4H_9)(C_3H_7)NCH_2CH_2CN$ | 61 | 16 |

| | | | | | |
|--------------------------------------|------|--------|---|------|-------|
| <i>sec</i> -Butyl- <i>n</i> -propyl- | 24 | 95 | (<i>sec</i> -C ₄ H ₉)(C ₃ H ₇)NCH ₂ CH ₂ CN | 34 | 16 |
| Isobutyl- <i>n</i> -propyl- ‡ | 24 | 95 | (<i>iso</i> -C ₄ H ₉)(C ₃ H ₇)NCH ₂ CH ₂ CN | 49 | 16 |
| 4-Heptyl-methyl- § | 24 | 95 | (C ₃ H ₇) ₂ NCH ₂ CH ₂ CH ₂ CN | 65 | 16 |
| Di- <i>n</i> -butyl- | — | 75 | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 64 | 1 |
| | 24* | 50 | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 91 | 2 |
| | 24* | 50 | (<i>n</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 90 | 2 |
| Diisobutyl- | 24* | 50 | (<i>iso</i> -C ₄ H ₉) ₂ NCH ₂ CH ₂ CN | 51 | 14 |
| <i>n</i> -Butyl- <i>sec</i> -butyl- | 24 | 95 | (<i>n</i> -C ₄ H ₉)(<i>sec</i> -C ₄ H ₉)NCH ₂ CH ₂ CN | 42 | 16 |
| Di- <i>n</i> -amyl- | 24 | 50 | (<i>n</i> -C ₅ H ₁₁) ₂ NCH ₂ CH ₂ CN | 90 | 2, 13 |
| Di- <i>n</i> -hexyl- | 24* | 50 | (<i>n</i> -C ₆ H ₁₃) ₂ NCH ₂ CH ₂ CN | 85 | 2 |
| Di- <i>n</i> -octyl- | 100* | 100 | (<i>n</i> -C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CN | 80 | 14 |
| Di-2-ethylhexyl- | 100* | 100 | (C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CN | 65 | 14 |
| Di-2-ethylhexyl- | — | — | (C ₈ H ₁₇) ₂ NCH ₂ CH ₂ CN | 77 | 2 |
| Di-(γ -diethylaminopropyl)- | 24* | 100 | (C ₃ H ₇) ₂ NCH ₂ CH ₂ CH ₂ NCH ₂ CH ₂ CN | 78 | 2 |
| γ -Diethylaminopropyl- | 24* | 50 | (C ₃ H ₇) ₂ NCH ₂ CH ₂ CH ₂ NHCH ₂ CH ₂ CN | 70.4 | 2 |
| Benzyl-methyl- | — | — | C ₆ H ₅ CH ₂ N(CH ₃)CH ₂ CH ₂ CN | 93 | 15 |
| Cyclopentyl-methyl- § | 24 | 95 | (C ₅ H ₉)(CH ₃)NCH ₂ CH ₂ CN | 96 | 16 |
| Cyclohexyl-methyl- § | 24 | 95 | (C ₆ H ₁₁)(CH ₃)NCH ₂ CH ₂ CN | 91 | 16 |
| Cyclopentyl-ethyl- | 24 | 95 | (C ₅ H ₉)(C ₂ H ₅)NCH ₂ CH ₂ CN | 48 | 16 |
| Cyclopentyl- <i>n</i> -butyl- § | 24 | 95 | (C ₅ H ₉)(<i>n</i> -C ₄ H ₉)NCH ₂ CH ₂ CN | 68 | 16 |
| <i>N</i> -Methylaniline ¶ | 4 | 180 | C ₆ H ₅ N(CH ₃)CH ₂ CH ₂ CN | 25 | 2 |
| <i>N</i> -Methylaniline ** | 12 | Reflux | C ₆ H ₅ N(CH ₃)CH ₂ CH ₂ CN | Good | 22 |

* Allowed to stand forty-eight hours at room temperature after heating

† Distilled immediately after heating

‡ Allowed to stand in refrigerator twenty-four hours after refluxing

§ With benzyltrimethyl ammonium hydroxide catalyst (Tetron B).

¶ With trace of Cu bronze.

¶ Hydrated copper sulfate catalyst.

** In glacial acetic acid as catalyst.

TABLE IV
CYANOETHYLATION OF SECONDARY HETEROCYCLIC AMINES

| Amine | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|----------------------------|--------------|-------------|---|------------|-----------|
| 2,2-Dimethyl-2-phenylamine | Reflux | 34 | $(CH_3)_2C \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} Cl \\ Cl \end{array} NCH_2CH_2CN$ | 66 | 18 |
| Morpholine | 50 | 21 * | N-(β -Cyanoethyl)morpholine | 95 | 2, 13 |
| Piperazine | — | 20 | bis-N,N'-(β -Cyanoethyl)piperazine | — | 20, 21 |
| Pyrrrole † | Reflux | 5 | N-(β -Cyanoethyl)pyrrrole | 44 | 20 |
| Pyrrrole ‡ | 40 § | 1 | N-(β -Cyanoethyl)pyrrrole | 80 | 27 |
| Pyrrrole | — | — | N-(β -Cyanoethyl)pyrrrole | 86 | 17 |
| Pyrrrolidine | — | — | N-(β -Cyanoethyl)pyrrrolidine | 81 | 17 |
| Piperidine | 8-20 | 16 | N-(β -Cyanoethyl)piperidine | 92 | 2, 20 |
| 2-Methylpiperidine | — | — | N-(β -Cyanoethyl)-2-methylpiperidine | 99 | 17 |
| 3-Methylpiperidine | — | — | N-(β -Cyanoethyl)-3-methylpiperidine | 97 | 17 |
| 4-Methylpiperidine | — | — | N-(β -Cyanoethyl)-4-methylpiperidine | 87 | 17 |
| 2,3-Dimethylpiperidine § | — | — | N-(β -Cyanoethyl)-2,3-dimethylpiperidine | 99 | 17 |
| 2,4-Dimethylpiperidine § | — | — | N-(β -Cyanoethyl)-2,4-dimethylpiperidine | 68 | 17 |
| 2,6-Dimethylpiperidine § | — | — | N-(β -Cyanoethyl)-2,6-dimethylpiperidine | 82 | 17 |
| Morpholinoethylamine | — | — | β -(Morpholinoethylamino)propionitrile | 81.5 | 2 |
| Morpholinopropylamine | — | — | β -(Morpholinopropylamino)propionitrile | 76 | 2 |
| Piperidine † | Reflux | 1.5 | N-(β -Cyanoethyl)piperidine | — | 20 |
| Leucin § | 30 | 48 | N-(β -Cyanoethyl)leucin | 50 | 26 |
| Indole † | 120-30 ¶ | 5 | 1-(β -Cyanoethyl)indole | 77 | 20 |
| 2-Methylindole † | 130 ¶ | 12-13 | 1-(β -Cyanoethyl)-2-methylindole | 74 | 20 |

| | | | | | |
|-------------------------------------|----------|---------|---|------|-------|
| 2,3-Dimethylindole † | 130-40 † | 12 | 1-(β -Cyanoethyl)-2,3-dimethylindole | 82 | 20 |
| 5-Methoxy-2,3-dimethylindole | 120-40 | 2 | 1-(β -Cyanoethyl)-2,3-dimethyl-5-methoxyindole | 84 | 20 |
| 2-Phenylindole ‡ | 60 | 24 ‡ ** | 1-(β -Cyanoethyl)-2-phenylindole | 80 | 27 |
| 2-Phenylindole † | 75 | 1-2 | 1-(β -Cyanoethyl)-2-phenylindole | 100 | 20 |
| 2-Methylindoline ** | 140 | 15 | N-(β -Cyanoethyl)-2-methylindoline | 100 | 22 |
| Benzimidazole † | 29-80 | 2 †† | 1-(β -Cyanoethyl)benzimidazole | 93 | 20 |
| Indole-3-aldehyde † | 30 | 24 ‡ | 1-(β -Cyanoethyl)indole-3-aldehyde | 70 | 27 |
| 2-Methylindole-3-aldehyde † | 30 | 24 ‡ | 1-(β -Cyanoethyl)-2-methylindole-3-aldehyde | — | 27 |
| 2-Phenylindole-3-aldehyde † | 30 | 72 ‡ | 1-(β -Cyanoethyl)-2-phenylindole-3-aldehyde | 90 | 27 |
| Tetrahydroquinoline ** | 108-125 | 6 | N-(β -Cyanoethyl)tetrahydroquinoline | 75.5 | 2, 22 |
| Decahydroquinoline † | 200 | 2 | N-(β -Cyanoethyl)decahydroquinoline | 60 | 20 |
| Carbazole † | 75 | 1 | N-(β -Cyanoethyl)carbazole | 75 | 20 |
| Carbazole ‡ | 0-100 | 1 | N-(β -Cyanoethyl)carbazole | 85.4 | 2 |
| 1,2,3,4,10,11-Hexahydrocarbazole ** | 130 | 12 | N-(β -Cyanoethyl)hexahydrocarbazole | Good | 22 |

* Allowed to stand forty-eight hours at room temperature after heating.

† With sodium ethoxide catalyst.

‡ In dioxane.

§ With Trizon B catalyst.

|| In ethanol.

¶ In sealed tube.

** In glacial acetic acid as catalyst.

†† In pyridine.

| | | | | | |
|-------------------------------------|----------|---------|---|------|-------|
| 2,3-Dimethylindole † | 130-40 † | 12 | 1-(β -Cyanoethyl)-2,3-dimethylindole | 82 | 20 |
| 5-Methoxy-2,3-dimethylindole | 120-40 | 2 | 1-(β -Cyanoethyl)-2,3-dimethyl-5-methoxyindole | 84 | 20 |
| 2-Phenylindole ‡ | 60 | 24 ‡ ** | 1-(β -Cyanoethyl)-2-phenylindole | 80 | 27 |
| 2-Phenylindole † | 75 | 1-2 | 1-(β -Cyanoethyl)-2-phenylindole | 100 | 20 |
| 2-Methylindoline ** | 140 | 15 | N-(β -Cyanoethyl)-2-methylindoline | 100 | 22 |
| Benzimidazole † | 29-80 | 2 †† | 1-(β -Cyanoethyl)benzimidazole | 93 | 20 |
| Indole-3-aldehyde ‡ | 30 | 24 ‡ | 1-(β -Cyanoethyl)indole-3-aldehyde | 70 | 27 |
| 2-Methylindole-3-aldehyde ‡ | 30 | 24 ‡ | 1-(β -Cyanoethyl)-2-methylindole-3-aldehyde | — | 27 |
| 2-Phenylindole-3-aldehyde ‡ | 30 | 72 ‡ | 1-(β -Cyanoethyl)-2-phenylindole-3-aldehyde | 90 | 27 |
| Tetrahydroquinoline ** | 108-125 | 6 | N-(β -Cyanoethyl)tetrahydroquinoline | 75.5 | 2, 22 |
| Decahydroquinoline † | 200 | 2 | N-(β -Cyanoethyl)decahydroquinoline | 60 | 20 |
| Carbazole † | 75 | 1 | N-(β -Cyanoethyl)carbazole | 75 | 20 |
| Carbazole ‡ | 0-100 | 1 | N-(β -Cyanoethyl)carbazole | 85.4 | 2 |
| 1,2,3,4,10,11-Hexahydrocarbazole ** | 120 | 12 | N-(β -Cyanoethyl)hexahydrocarbazole | Good | 22 |

* Allowed to stand forty-eight hours at room temperature after heating.

† With sodium ethoxide catalyst.

‡ In dioxane.

§ With Triton B catalyst.

|| In ethanol.

¶ In sealed tube.

** In glacial acetic acid as catalyst.

†† In pyridine.

TABLE V
CYANOETHYLATION OF AMIDES, IMIDES, LACTAMS, AND SULFONAMIDES

| Compound | Catalyst | Product | Yield, % | References |
|--|----------|--|----------|------------|
| Formamide | Na | $\text{HCNHCCH}_2\text{CH}_2\text{CN}$ | — | 28, 30 |
| Formamide | NaOH | $\text{HCN}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 28, 29 |
| Acetamide | NaOH | $\text{CH}_3\text{CONHCCH}_2\text{CH}_2\text{CN}$ | 72 | 30 |
| Acetamide | Trilon B | $\text{CH}_3\text{CON}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 38 |
| N-n-Propylformamide | NaOH | $\text{HCN}(\text{C}_3\text{H}_7\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| N-n-Butylformamide | NaOH | $\text{HCN}(\text{C}_4\text{H}_9\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| N-n-Hexylformamide | NaOH | $\text{HCN}(\text{C}_6\text{H}_{13}\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| N-cyclohexylformamide | NaOH | $\text{HCN}(\text{C}_6\text{H}_{11}\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| N-phenylformamide | NaOH | $\text{HCN}(\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| N-methylacetamide | NaOH | $\text{CH}_3\text{CON}(\text{CH}_3\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30, 31 |
| N-ethylpropionamide | NaOH | $\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30, 31 |
| Benamide | NaOH | $\text{C}_6\text{H}_5\text{CONHCCH}_2\text{CH}_2\text{CN}$ | — | 31 |
| Acetanilide | NaOH | $\text{CH}_3\text{CON}(\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 31 |
| Crotanamide | Trilon B | $\text{NCCH}_2\text{CH}=\text{CHCON}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 32, 33 |
| N,N'-Dimethyladipamide | NaOH | $\text{NCCH}_2\text{CH}_2(\text{CH}_2)_4\text{NCO}(\text{CH}_2)_4\text{CON}(\text{CH}_2)_4\text{CH}_2\text{CH}_2\text{CN}$ | — | 31 |
| Succinimide | NaOH | N-(β -Cyanoethyl)succinimide | — | 30 |
| Phthalimide | Trilon B | N-(β -Cyanoethyl)phthalimide | — | 31 |
| α -Pyrrolidone | NaOH | N-(β -Cyanoethyl)pyrrolidone | 100 | 31 |
| ϵ -Caprolactam | NaOH | N-(β -Cyanoethyl)caprolactam | — | 30, 31 |
| 2-Pyrrolone | NaOH | N-(β -Cyanoethyl)pyrrolone | 95 | 35 |
| Propanesulfonmethylanilide | NaOH | $\text{CH}_3\text{CH}_2\text{CH}_2\text{SO}_2\text{N}(\text{CH}_3\text{CH}_2\text{CH}_2\text{CN})_2$ | 95 | 30 |
| Butanesulfonamide | Trilon B | $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{NHCCH}_2\text{CH}_2\text{CN}$ | 51 | 38 |
| Benzenesulfonamide | Trilon B | $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 55 | 38 |
| Benzoylsulfonamide | Trilon B | $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 90 | 36, 37 |
| Benzoylsulfonamide | NaOH | $\text{C}_6\text{H}_5\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 30 |
| p-Acetylbis(benzenesulfon)yl-N-methylamide | NaOH | $\text{CH}_3\text{CONHC}_6\text{H}_4\text{SO}_2\text{N}(\text{CH}_2)_4\text{CH}_2\text{CH}_2\text{CN}$ | — | 30 |

TABLE VI
CYANOETHYLATION OF MONOHYDRIC AND POLYHYDRIC ALCOHOLS

| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Refer- ence |
|--------------------|-------------------------------------|--------------|-------------|---|------------|----------------|
| Methanol | Triton B or CH_3ONa | — | — | $\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 89 | 44 |
| Methanol | CH_3ONa | 30-35 | 1.5 | " | — | 41 |
| Methanol | 2% NaOH solution | — | — | " | 90 | 48 |
| Ethanol | 2% NaOH solution | — | — | " | 90 | 48 |
| Ethanol | NaOH | 35-70 | 0.25 | " | — | 41 |
| Ethanol | NaOCH_3 or Triton B | — | — | " | 78 | 44 |
| Ethanol | NaOCH_3 | — | — | " | 89 | 42 |
| 2-Propanol | NaOH | 30-35 | — | " | — | 41 |
| 2-Propanol | NaOCH_3 or Triton B | 60-80 | 1 | $120\text{-C}_3\text{H}_7\text{OCH}_2\text{CH}_2\text{CN}$ | — | 44 |
| 2-Propanol | NaOH | — | — | " | 69 | 44 |
| 1-Butanol | NaOCH_3 or Triton B | — | — | " | 85 | 48 |
| 1-Butanol | KOH | — | — | " | 88 | 48 |
| 1-Butanol | KOH | 25-45 | 2 | $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{CN}$ | 86 | 44 |
| 1-Butanol | Triton B | 40 | — | " | — | 43 |
| 1-Butanol | Na | 30-35 | 12 | " | 82 | 41 |
| tert-Butyl alcohol | NaOH | 80 | — | " | — | 41 |
| 1-Pentanol | Na | — | — | $tert\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{CN}$ | 92 | 48 |
| 1-Pentanol | Na | 35-40 | 16 | $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{CN}$ | 86 | 41 |
| 2-Ethyl-1-hexanol | Na | 30-35 | — | " | — | 41 |
| 2-Ethyl-1-hexanol | Na | 75 | 1 | $\text{C}_6\text{H}_{13}\text{OCH}_2\text{CH}_2\text{CN}$ | 88 | 48 |
| 2-Ethyl-1-hexanol | NaOCH_3 | — | — | " | 77 | 44 |
| 1-Octanol | Na | — | — | " | 80 | 48 |
| 1-Decanol | Na | 50 | 15 | $n\text{-C}_{10}\text{H}_{21}\text{OCH}_2\text{CH}_2\text{CN}$ | 37 | 48 |
| 1-Dodecanol | NaOC_2H_5 | 50-55 | 1 | $n\text{-C}_{12}\text{H}_{25}\text{OCH}_2\text{CH}_2\text{CN}$ | — | 41 |
| 1-Octadecanol | NaOC_2H_5 | 75 | — | $n\text{-C}_{18}\text{H}_{37}\text{OCH}_2\text{CH}_2\text{CN}$ | — | 41 |
| Benzyl alcohol | NaOCH_3 | — | — | $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 94 | 44 |

TABLE VI—Continued
CYANOETHYLATION OF MONOHYDRIC AND POLYHYDRIC ALCOHOLS

| Alcohol | Catalyst | Temp. °C. | Time hr. | Product | Yield % | Refer- ence |
|-------------------------------|----------------|--------------|-------------|---|------------|----------------|
| Cyclohexanol | — | — | — | $C_6H_{11}OCH_2CH_2CN$ | — | 43 |
| 3,5-Dimethylcyclohexanol | $NaOCH_3$ | 75 | — | $(CH_3)_2C_6H_9OCCH_2CH_2CN$ | 51 | 44 |
| Ethylene glycol | $NaOCH_3$ | 40-50 | 3 | $NOCH_2CH_2OC_2H_4OCCH_2CH_2CN$ | — | 41, 52 |
| 1,2-Ethylene glycol | $NaOCH_3$ | 25-30 | 0 | — | 83 | 37, 50 |
| Propylene glycol | $NaOCH_3$ | 25-30 | 6 | $NCC_2H_4OCCH_2CH_2CH_2OC_2H_4CN$ | 78 | 37, 50 |
| Trimethylene glycol | $NaOCH_3$ | 25-30 | 6.5 | $NCC_2H_4O(CH_2)_3OC_2H_4CN$ | 87 | 37, 50 |
| 2,3-Butylene glycol | $NaOCH_3$ | 20-25 | 6 | $NCC_2H_4OCH(CH_3)CH(CH_3)OC_2H_4CN$ | 67 | 37, 50 |
| 1,3-Butylene glycol | $NaOCH_3$ | 25 | 7 | $NCC_2H_4OCCH_2CH_2CH_2CH_2OC_2H_4CN$ | 68 | 37, 50 |
| Pentamethylene glycol | $NaOCH_3$ | 25 | 6 | $NCC_2H_4O(CH_2)_5OC_2H_4CN$ | 80 | 37, 50 |
| Decamethylene glycol | $NaOCH_3$ | 25 | 6 | $NCC_2H_4O(CH_2)_{10}OC_2H_4CN$ | 80 | 37, 50 |
| 1,12-Dihydroxydodecane | $NaOCH_3$ | 40-45 | 5.5 | $CH_3(CH_2)_8CH(CH_2)_{10}CH_2OC_2H_4CN$ | — | 50 |
| $(CH_3)_2C(OH)CH_2OH$ | $NaOCH_3$ | 25 | 5.5 | $(CH_3)_2C(OH)CH_2OCCH_2CH_2CN$ | 71 | 50 |
| $(CH_3)_2C(OH)CH_2CH(OH)CH_3$ | $NaOCH_3$ | 25 | 5.5 | $(CH_3)_2C(OH)CH_2CH(CH_3)OC_2H_4CN$ | 58 | 50 |
| 1,2-Cyclohexanediol | $NaOCH_3$ | 25 | 7 | $ \begin{array}{c} CH_3 \quad \quad \quad CH_3 \\ \diagdown \quad \diagup \\ CH_2-CHOC_2H_4CN \\ \diagup \quad \diagdown \\ CH_3 \quad \quad \quad CH_3 \end{array} $ | 60 | 50 |
| Glycerol | $NaOCH_3$ | 25 | 6 | $ \begin{array}{c} CH_2-CH_2-CH_3 \\ \quad \quad \\ CH_2OC_2H_4CN \quad CHOC_2H_4CN \\ \quad \quad \\ CHOC_2H_4CN \quad CHOC_2H_4CN \end{array} $ | 74 | 37, 50 |
| Pentaerythritol | Aqueous $NaOH$ | 40-50 | 7 | $CH_2OC_2H_4CN$ | — | 50 |
| Mannitol | Aqueous $NaOH$ | 40-50 | 5 | $ \begin{array}{c} C(CH_2OCCH_2CH_2CN)_4 \\ \text{Hexm-(}\beta\text{-cyanoethoxy)hexano} \end{array} $ | — | 50 |

TABLE VII

CYANOETHYLATION OF UNSATURATED ALCOHOLS AND ETHER ALCOHOLS

| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|---|--------------------|--------------|-------------|---|------------|-----------|
| Allyl — | NaOH | 45-60 | 3.5 | $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 41 |
| Allyl — | Na ₂ O | 15-25 | 7 | | — | 49 |
| Methylal — | Na ₂ O | 15-25 | 7 | $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 70 | 49 |
| Vinyl dimethyl carbinol | NaOCH ₃ | 10-20 | 0 | $\text{CH}_2=\text{CHC}(\text{CH}_3)_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 49 |
| Ethynyl dimethyl carbinol | NaOCH ₃ | 17-25 | 7 | $\text{HC}\equiv\text{CC}(\text{CH}_3)_2\text{OCH}_2\text{CH}_2\text{CN}$ | 72 | 49 |
| Geraniol | Na ₂ O | 25 | 7 | $\text{C}_{10}\text{H}_{17}\text{OCH}_2\text{CH}_2\text{CN}$ | 60 | 49 |
| Linalool | Na ₂ O | 25-28 | 7 | $\text{C}_{10}\text{H}_{17}\text{OCH}_2\text{CH}_2\text{CN}$ | — | 49 |
| Citronellol | NaOCH ₃ | 25 | 7 | $\text{C}_{10}\text{H}_{17}\text{OCH}_2\text{CH}_2\text{CN}$ | 77 | 49 |
| Cinnamyl — | NaOCH ₃ | 25 | 6.5 | $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 73 | 49 |
| Oleyl — | Na ₂ O | 20-25 | 7 | $\text{C}_{18}\text{H}_{33}\text{OCH}_2\text{CH}_2\text{CN}$ | 45 | 49 |
| Furfuryl — | Na ₂ O | 20-30 | 8 | β -(Furfuryloxy)propionitrile | 67 | 49 |
| $\text{CH}_2=\text{CH}-\text{CH}(\text{OCH}_2\text{CH}_2\text{CN})_2$ | Na | 25 | 0.5 | $\text{CH}_2=\text{CH}-\text{CH}(\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN})_2$ | 40 | 56 |
| $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH ₃ | 18-20 | 2 | $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 80 | 56 |
| $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{OH}$ | Na | 15-25 | 1 | $\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OCH}_2\text{CH}_2\text{CN}$ | 80 | 56 |
| Tetrahydrofurfuryl — | NaOCH ₃ | 75 | — | $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{OCH}_2\text{CH}_2\text{CN})_2$ | 80 | 44 |
| Tetrahydrofurfuryl — | Na ₂ O | 15-25 | 6 | — | 44.5 | 46 |

TABLE VII—Continued
CYANOETHYLATION OF UNSATURATED ALCOHOLS AND ETHER ALCOHOLS

| Alcohol | Catalyst | Temp., °C. | Time, Hr. | Product | Yield % | Reference |
|---|---------------------------|---------------|--------------|--|------------|-----------|
| $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ | NaOC_2H_5 | 25 | 5 | $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 74 | 46 |
| $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 75 | — | $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 87 | 44 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | Na_2O | 25 | 8 | $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 46 |
| $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OH}$ | Triton B | 30–45 | 1 | $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 78 | 40 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 18 | $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 46 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | Triton B | 25–30 | 4 | $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 76 | 46 |
| $p\text{-tert-Amylphenoxyethanol}$ | Triton B | 25 | 18 | $p\text{-tert-C}_6\text{H}_4\text{H}_2\text{C}_6\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 67 | 46 |
| $p\text{-tert-Octylphenoxyethanol}$ | NaOCH_3 | 25–30 | 24 | $p\text{-tert-C}_6\text{H}_4\text{H}_2\text{C}_6\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 80 | 46 |
| $\text{CH}_3\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 7 | $\text{CH}_3\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 63 | 46 |
| $n\text{-C}_4\text{H}_9\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 8 | $n\text{-C}_4\text{H}_9\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 70 | 46 |
| Glyceryl 1,3-dimethyl ether | NaOCH_3 | 25–35 | 6 | $(\text{CH}_3\text{OCH}_2)_2\text{CHOCH}_2\text{CH}_2\text{CN}$ | 80 | 46 |
| Dioctylene glycol | 50% NaOH | 10–20 | 5 | $\text{NCC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 91 | 37, 50 |
| $\text{HOCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{OH}$ | NaOC_2H_5 | 25 | 7 | $\text{NCC}_2\text{H}_4\text{OC}_2\text{H}_4\text{SCH}_2\text{CH}_2\text{OC}_2\text{H}_4\text{CN}$ | 92 | 37, 50 |
| Triethylene glycol | NaOC_2H_5 | 25 | 16 | $\text{NCC}_2\text{H}_4(\text{OC}_2\text{H}_4)_3\text{OC}_2\text{H}_4\text{CN}$ | 77 | 37, 50 |
| Glyceryl α -methyl ether | NaOCH_3 | 25–30 | 0.5 | $\text{CH}_3\text{OCH}_2\text{CHOCH}_2\text{CH}_2\text{CN}$ | 61 | 50 |
| Glyceryl α -butyl ether | NaOCH_3 | 25–30 | 0.5 | $\text{C}_4\text{H}_9\text{OCH}_2\text{CHOCH}_2\text{CH}_2\text{CN}$ | 43 | 49 |
| Dipropylene glycol | NaOCH_3 | 25 | 17 | $\text{bis}(\beta\text{-Cyanoethoxy})\text{-2,2'-dipropyl ether}$ | 73 | 50 |

TABLE VIII
CYANOETHYLATION OF ALCOHOLS CONTAINING HALOGEN, NITRILE, OR OTHER FUNCTIONAL GROUPS


| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|---|------------------------------------|--------------|-------------|---|------------|-----------|
| $\text{ClCH}_2\text{CH}_2\text{OH}$ | 40% NaOH | 40 | 10 | $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 65 |
| $\text{FCH}_2\text{CH}_2\text{OH}$ | — | — | — | $\text{FCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 66 |
| $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ | NaOH | 20-35 | 2 | $\text{ClCH}_2\text{CH}_2\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 70 | 46 |
| p-Chlorophenoxymethanol | Triben D | 25-40 | 2 | $\text{ClC}_6\text{H}_4\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 72 | 46 |
| $\text{NOCH}_2\text{CH}_2\text{OH}$ | Na | 40-45 | 3 | $\text{NOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 41 |
| $\text{NOCH}_2\text{CH}_2\text{OH}$ | 20% KOH | 25-40 | 18 | $\text{NOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 91 | 37 |
| $\text{NOCH}_2\text{CH}_2\text{OH}$ | KCN | 80 | 0.2 | $\text{NOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 62 |
| NOCH_2OH | $(\text{C}_2\text{H}_5)_3\text{N}$ | 80-90 | 0.75 | $\text{NOCH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 62 |
| CH_3CHOHCN | NaOH | 90 | 0.5 | $\text{CH}_3\text{CH}(\text{CN})\text{OCH}_2\text{CH}_2\text{CN}$ | — | 62 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 67 | 67 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 80 | 2 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75.4 | 2 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CHOHCN}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{N}(\text{CH}_2)_3\text{CH}(\text{CH}_3)\text{OC}_2\text{H}_4\text{CN}$ | 66 | 2 |
| N-2-Hydroxyethylmorpholine | NaOCH_3 | 25 | 19 |  | 43 | 67 |

TABLE VII—Continued
CYANOMETHYLATION OF UNSATURATED ALCOHOLS AND BLENDED ALCOHOLS

| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|---|---------------------------|--------------|-------------|--|------------|-----------|
| $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ | NaOC_2H_5 | 25 | 5 | $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 74 | 46 |
| $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 75 | — | $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 87 | 44 |
| $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | Na_2O | 25 | 8 | $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 46 |
| $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OH}$ | Triton B | 30–45 | 1 | $n\text{-C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 78 | 46 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 18 | $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 46 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$ | Triton B | 25–30 | 4 | $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 76 | 46 |
| $p\text{-tert-Amylphenoxylethanol}$ | Triton B | 25 | 18 | $p\text{-tert-C}_4\text{H}_9\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 97 | 46 |
| $p\text{-tert-Octylphenoxylethanol}$ | NaOCH_3 | 25–30 | 24 | $p\text{-tert-C}_8\text{H}_{17}\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 80 | 46 |
| $\text{CH}_3\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 7 | $\text{CH}_3\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 63 | 46 |
| $n\text{-C}_4\text{H}_9\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 8 | $n\text{-C}_4\text{H}_9\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 70 | 46 |
| Glycerol 1,3-dimethyl ether | NaOCH_3 | 25–35 | 6 | $(\text{CH}_3\text{OCH}_2)_2\text{CHOC}_2\text{H}_4\text{CN}$ | 80 | 46 |
| Dibutylene glycol | 50% NaOH | 10–20 | 5 | $\text{NCC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{OC}_2\text{H}_4\text{CN}$ | 91 | 37, 50 |
| $\text{HOCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{OH}$ | NaOC_2H_5 | 25 | 7 | $\text{NCC}_2\text{H}_4\text{OC}_2\text{H}_4\text{SCH}_2\text{CH}_2\text{OC}_2\text{H}_4\text{CN}$ | 92 | 37, 50 |
| Triethyleno glycol | NaOC_2H_5 | 25 | 16 | $\text{NCC}_2\text{H}_4(\text{OC}_2\text{H}_4)_3\text{OC}_2\text{H}_4\text{CN}$ | 77 | 37, 50 |
| Glycerol α -methyl ether | NaOCH_3 | 25–30 | 0.5 | $\text{CH}_3\text{OCH}_2\text{CHOC}_2\text{H}_4\text{CN}$ | 61 | 50 |
| | | | | $\text{CH}_3\text{OC}_2\text{H}_4\text{CN}$ | | |
| Glycerol α -butyl ether | NaOCH_3 | 25–30 | 0.5 | $\text{C}_4\text{H}_9\text{OCH}_2\text{CHOC}_2\text{H}_4\text{CN}$ | 43 | 49 |
| | | | | $\text{C}_4\text{H}_9\text{OC}_2\text{H}_4\text{CN}$ | | |
| Dipropylene glycol | NaOCH_3 | 25 | 17 | $\text{bis}(\beta\text{-Cyanomethoxy})\text{-2,2'-dipropyl ether}$ | 73 | 50 |

TABLE VIII
CYANOETHYLATION OF ALCOHOLS CONTAINING HALOGEN, NITRILE, OR OTHER FUNCTIONAL GROUPS


| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|---|------------------------------------|--------------|-------------|---|------------|-----------|
| $\text{ClCH}_2\text{CH}_2\text{OH}$ | 40% NaOH | 40 | 10 | $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 65 |
| $\text{FCH}_2\text{CH}_2\text{OH}$ | — | — | — | $\text{FCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 66 |
| $\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ | NaOH | 20-35 | 2 | $\text{ClCH}_2\text{CH}_2\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 70 | 46 |
| p-Chlorophenoxyethanol | Triton B | 25-40 | 2 | $\text{ClC}_6\text{H}_4\text{OC}_2\text{H}_4\text{OCH}_2\text{CH}_2\text{CN}$ | 72 | 46 |
| $\text{NCCl}_2\text{CH}_2\text{OH}$ | Na | 40-45 | 3 | $\text{NCCl}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 41 |
| $\text{NCCl}_2\text{CH}_2\text{OH}$ | 20% KOH | 25-40 | 18 | $\text{NCCl}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 91 | 37 |
| $\text{NCCl}_2\text{CH}_2\text{OH}$ | KCN | 80 | 0.2 | $\text{NCCl}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 75 | 62 |
| NCCl_2OH | $(\text{C}_4\text{H}_9)_3\text{N}$ | 80-90 | 0.75 | $\text{NCCl}_2\text{OCH}_2\text{CH}_2\text{CN}$ | — | 62 |
| CH_3CHOHCN | NaOH | 90 | 0.5 | $\text{CH}_3\text{CH}(\text{CN})\text{OCH}_2\text{CH}_2\text{CN}$ | — | 62 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 67 | 67 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 80 | 2 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_4\text{CN}$ | 75.4 | 2 |
| $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CHOHCN}$ | NaOCH_3 | 25 | 24 | $(\text{C}_2\text{H}_5)_2\text{N}(\text{CH}_2)_2\text{CH}(\text{CN})\text{OC}_2\text{H}_4\text{CN}$ | 66 | 2 |
| N-(β -Hydroxyethyl)morpholine | NaOCH_3 | 25 | 18 |  | 43 | 67 |

TABLE VIII—Continued
CYANOETHYLATION OF ALCOHOLS CONTAINING HALOGEN, NITRILE, OR OTHER FUNCTIONAL GROUPS

| Alcohol | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|---|--|--------------|-------------|---|------------|-----------|
| N-(β -Hydroxyethyl)di-2-ethyl- hoxylamino | NaOCH_3 | 55 | 1 | $(\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 47 | 67 |
| C_6H_5 C_2H_5 CH_3 $\text{NCH}_2\text{CH}_2\text{OH}$ | NaOCH_3 | 25 | 18 | $\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 66.5 | 67 |
| CH_3 CH_3 $\text{NCH}_2\text{CHOHCH}_2\text{OH}$ | NaOH aqueous | 45 | 4 | $(\text{CH}_3)_2\text{NCH}_2\text{CHOC}_2\text{H}_4\text{CN}$ $\text{OCH}_2\text{CH}_2\text{CN}$ | 37 | 67 |
| CH_3 CH_3 $\text{NCH}_2\text{CHOHCH}_2\text{OH}$ | NaOCH_3 | 25 | 21 | $(\text{CH}_3)_2\text{NCH}_2\text{CHOC}_2\text{H}_4\text{CN}$ $\text{CH}_3\text{OC}_2\text{H}_4\text{CN}$ | 37 | 67 |
| Triethanolamine Triisopropylamine | NaOCH_3 KOC_2H_5 | 20–10 25 | 16 18 | $\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN})_3$ $\text{N}(\text{CH}_2\text{CH}(\text{CH}_3)\text{OCH}_2\text{CH}_2\text{CN})_3$ | 97 — | 67 67 |

TABLE IX
CYANOTRITRATION OF PHENOLS, OXIMES, HYDROGEN SULFIDE, MERCAPTANS, AND THIOPHENOLS

| Compound | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Refer- ence |
|-------------------------|--------------------|--------------|-------------|--|------------|----------------|
| Phenol | Na | 130-40 | 4-6 | $C_6H_5OCH_2CH_2CN$ | — | 70 |
| Phenol | Triton B | Reflux | 20 | $C_6H_5OCH_2CH_2CN$ | 67.5 | 73 |
| m-Chlorophenol | Na | 120-30 | 3 | β -(3-Chlorophenoxy)propionitrile | — | 70 |
| m-Methoxyphenol | Triton B | Reflux | 20 | β -(3-Methoxyphenoxy)propionitrile | 70.5 | 73 |
| Pyrocatechol | Na | 130-40 | 5 | β -(2-Hydroxyphenoxy)propionitrile | — | 70 |
| Resorcinol | Triton B | Reflux | 20 | 1,3-Di-(β -cyanoethoxy)benzene | 40 | 73 |
| Hydroquinone | Na | 120-30 | 5 | 1,4-Di-(β -cyanoethoxy)benzene | — | 70 |
| Salicylaldehyde | Triton B | Reflux | 30 | 2-(β -Cyanoethoxy)benzaldehyde | 1.3 | 73 |
| Salicylaldehyde | Triton B | Reflux | 30 | 3-Cyano-1,2-benzopyran | 1.3 | 73 |
| Salicylaldehyde | Triton B | Reflux | 30 | 3-Cyano-4-chromanone | 2 | 73 |
| β -Naphthol | Na | Reflux | 3 | β -(2-Naphthoxy)propionitrile | — | 70 |
| β -Naphthol | NaOH (excess) | 30 | 2 | 2-Hydroxy-1-(2-cyanoethyl)naphthalene | 94 | 71 |
| β -Naphthol | Triton B | Reflux | 18 | β -(2-Naphthoxy)propionitrile | 79.2 | 74 |
| 6-Bromo-2-naphthol | Triton B | Reflux | 20 | 3-(6'-Bromo-2'-naphthoxy)propionitrile | 10 | 73 |
| Acetone oxime | NaOCH ₃ | 25-50 | 12 | $(CH_3)_2C=NOCH_2CH_2CN$ | 61 | 37 |
| Methyl ethyl ketoxime | NaOCH ₃ | 25 | 18 | $CH_3CH_2C=NOCH_2CH_2CN$ | — | — |
| Methyl n-butyl ketoxime | NaOCH ₃ | 25-30 | 20 | $CH_3CH_2CH_2C=NOCH_2CH_2CN$ | 71 | 37 |
| | | | | $CH_3CH_2CH_2C=NOCH_2CH_2CN$ | 82 | 75 |

TABLE IX—Continued
CYANOMETHYLATION OF PHENOLS, OXIMES, HYDROGEN SULFIDE, MERCAPTANS, AND THIOPHENOLS

| Compound | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Refer- ence |
|---|--------------------|--------------|-------------|---|------------|----------------|
| Acetophenone oxime | Triton B | -10-50 | 2 | $ \begin{array}{c} \text{C}_6\text{H}_5 \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \\ \diagdown \quad \diagup \\ \text{CH}_2-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \end{array} $ | 92 | 37 |
| Cyclohexanone oxime | NaOCH ₃ | 25 | 24 | $ \begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \\ \diagdown \quad \diagup \\ \text{CH}_2 \quad \text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \end{array} $ | — | 75 |
| Dimethylglyoxime | NaOH | 25 | 24 | $ \begin{array}{c} \text{CH}_3\text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \\ \text{C}_2\text{H}_5 \end{array} $ | 60 | 37 |
| α -Ethyl- β -propiolactone oxime | NaOCH ₃ | 25 | 19 | $ \begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CCH}_2\text{CN} \\ \text{C}_2\text{H}_5 \end{array} $ | 80 | 75 |
| α -Ethylhexaldioxime | Triton B | 25 | 4 | $ \begin{array}{c} \text{CH}_3(\text{CH}_2)_3\text{CHCH}=\text{CCH}_2\text{CN} \\ \text{CH}-\text{CH} \\ \text{O} \end{array} $ | — | 75 |
| Furfuraldioxime (syn) | NaOCH ₃ | 25 | 2 | $ \begin{array}{c} \text{CH}=\text{CCH}=\text{NOCH}_2\text{CH}_2\text{CN} \\ \text{O} \end{array} $ | 45 | 37 |
| Benzoin oxime | Triton B | 25 | 24 | $ \begin{array}{c} \text{C}_6\text{H}_5\text{C}=\text{NOCH}_2\text{CH}_2\text{CN} \\ \text{C}_6\text{H}_5\text{CH}=\text{CCH}_2\text{CH}_2\text{CN} \end{array} $ | 96 | 37 |

TABLE IX—Continued
CYANOETHYLATION OF PHENOLS, OXIMES, HYDROXYN SULFIDES, MERCAPTANS, AND THIOPHENOLS

| Compound | Catalyst | Temp. °C. | Time hr. | Product | Yield % | Refer- ence |
|-------------------|--------------------|--------------|-------------|---|------------|----------------|
| β -Naphthol | NaOH | 31–33 | 16 | $C_{10}H_7SOCH_2CH_2CN$ | — | 80 |
| 2-Mercaptoethanol | None | 25 | 16 | $HOCH_2CH_2SCH_2CH_2CN$ | 91 | 57 |
| 2-Mercaptoethanol | Triton B | 25 | 16 | $NCCH_2CH_2OC_2H_4SCH_2CH_2CN$ | 93.6 | 57 |
| 2-Mercaptoethanol | NaOH in Ethanol | 25 | 16 | $NCCH_2CH_2OC_2H_4SCH_2CH_2CN$ | 98.3 | 57 |
| 2-Mercaptoethanol | Piperidine | — | — | $NCCH_2CH_2SC_2H_4SCH_2CH_2CN$ | — | 81 |
| 2-Mercaptoethanol | Piperidine | — | — | $HSCH_2CH_2SCH_2CH_2CN$ | 26 | 81 |
| 2-Mercaptoethanol | None | — | — | $(C_2H_5)_2NCH_2CH_2SCH_2CH_2CN$ | 92 | 81 |
| 2-Mercaptoethanol | — | <30 | 3 | $(CH_3)_2NCSSCH_2CH_2CN$ | — | 80 |
| 2-Mercaptoethanol | — | <30 | — | $(C_2H_5)_2NCSSCH_2CH_2CN$ | 82.5 | 80 |
| 2-Mercaptoethanol | — | <40 | 3 | $C_6H_{10}NCSSCH_2CH_2CN$ | 61 | 80 |
| 2-Mercaptoethanol | — | 25 | 2 | 2-(β -Cyanoethylmercapto)benzothiazole | — | 80 |
| 2-Mercaptoethanol | — | Reflux | 0.5 | 2-(β -Cyanoethylmercapto)benzothiazole | 63 | 83 |
| 2-Mercaptoethanol | NaOH | <35 | 16 | 2-(β -Cyanoethylmercapto)thiazoline | 87 | 57 |
| 2-Mercaptoethanol | Triton B | <30 | 2 | 2-(β -Cyanoethylmercapto)thiazoline | 70 | 80 |
| 2-Mercaptoethanol | — | <30 | 2 | 2-(β -Cyanoethylmercapto)-1-methylthiazole | — | 80 |
| 2-Mercaptoethanol | — | <35 | 16 | 2-(β -Cyanoethylmercapto)benzoxazole | 88 | 57 |

TABLE X
CYANOETHYLATION OF ALDEHYDES AND KETONES

| Compound | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Refer- ence |
|---|----------|--------------|-------------|---|------------|----------------|
| Formaldehyde | NaOH | Reflux | 8 | $\text{NCCH}_2\text{CH}_2\text{OCH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 30 | 68 |
| Acetaldehyde | NaOH | Reflux | 1 | γ -Cyanobutyraldehyde | 40-50 | 116 |
| Propionaldehyde | NaOH | Reflux | 1 | γ -Formylpimelonitrile | 4.9 | 116 |
| Isobutyraldehyde | NaOH | 65-80 | 2 | $\text{CH}_3\text{C}(\text{CHO})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 25.1 | 116 |
| Isobutyraldehyde | NaCN | 80-90 | 2 | $(\text{CH}_3)_2\text{C}(\text{CHO})\text{CH}_2\text{CH}_2\text{CN}$ | 35-40 | 116 |
| 2-Ethylbutyraldehyde | KOH | 55-60 | 1 | $(\text{CH}_3)_2\text{C}(\text{CHO})\text{CH}_2\text{CH}_2\text{CN}$ | 50 | 114, 117 |
| 2-Ethylhexaldehyde | KOH | 55-60 | 1 | $(\text{C}_2\text{H}_5)_2\text{C}(\text{CHO})\text{CH}_2\text{CH}_2\text{CN}$ | 76.6 | 114, 118 |
| α -Ethyl- δ -propylacrolein | KOH | 45-55 | 1 | $(\text{C}_2\text{H}_5)_2\text{C}(\text{CHO})\text{CH}_2\text{CH}_2\text{CN}$ | 79 | 114, 118 |
| Acetone | KOH | 0-5 | 2 | $\text{CH}_3\text{CH}_2\text{CH}=\text{CHC}(\text{C}_2\text{H}_5)(\text{CHO})\text{CH}_2\text{CH}_2\text{CN}$ | 49 | 118 |
| Acetone | NaOH | Reflux | 5-7 | $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 77 | 103, 105 |
| $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2$ | Triton B | 40 | 2 | $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 8.5 | 104 |
| Methyl ethyl ketone | KOH | 5-10 | 2 | $\text{CH}_3\text{COC}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 89 | 103 |
| Methyl ethyl ketone | Na | 30-40 | 2 | $\text{CH}_3\text{COC}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 50 | 103 |
| $\text{CH}_3\text{COC}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})_2$ | Triton B | 25-40 | 48 | $(\text{NCCH}_2\text{CH}_2)_2\text{CHCOC}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 50 | 106 |
| Methyl n-propyl ketone | Triton B | 15 | 1 | $\text{CH}_3\text{COC}(\text{C}_2\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 43 | 103 |
| Methyl n-propyl ketone | Triton B | 15 | 1 | $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{COC}(\text{C}_2\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 103 |
| Methyl isobutyl ketone | KOH | 5-10 | 2 | $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 20 | 103 |
| Methyl n-amyl ketone | KOH | 5-10 | 2 | $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{C}_4\text{H}_9$ | 50 | 103 |
| Methyl n-hexyl ketone | KOH | 5-10 | 2 | $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{C}_5\text{H}_{11}$ | 50 | 103 |
| Diethyl ketone | Triton B | 30 | 24 | 2,4,4-tris(2-cyanoethyl)-3-pentanone | — | 103 |

TABLE X—*Continued*

| CYANOETHYLATION OF ALKENES AND KETONES | | | | | Yield % | Refer- ence |
|--|----------|--------------|-------------|--|---------------|----------------|
| Compound | Catalyst | Temp. °C. | Time Hr. | Product | | |
| Diisopropyl ketone | Triton B | 25 | 2 | $(\text{CH}_3)_2\text{CHCOC}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CN}$ $\text{NCCH}_2\text{CH}_2(\text{CH}_2)_2\text{COC}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CN}$ $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2$ | 40 | 107 |
| Acetonylacetone | Triton B | 25 | 20 | $\text{CH}_3\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 107 |
| Mesityl oxide | Triton B | 5-10 | 2 | $(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_2\text{CH}_2\text{CN})\text{COCCH}_3$ $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{CH}_2\text{CH}_2\text{CN})_2\text{COCCH}_3$ | 10-15 73.5 | 33 |
| Phorone | Triton B | 25 | 20 | Mono-cyanoethyl derivative | 24 | 107 |
| Methyl benzyl ketone | Triton B | 20-25 | 1 | Di-cyanoethyl derivative | 10 | — |
| Phoxylbenzoin | Triton B | 45 | 3 | $\text{CH}_3\text{COC}(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 86 | 103 |
| 2-Acetylcyclopentanone | Triton B | 30 | 24 | $\text{C}_6\text{H}_5\text{COC}(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 95 | 103 |
| 2-Propionylcyclopentanone | Triton B | 30 | 24 | 2-(β -Cyanoethyl)-2-acetylcyclopentanone | 67 | 32 |
| 2-Butyrylcyclopentanone | Triton B | 30 | 24 | 2-(β -Cyanoethyl)-2-propionylcyclopentanone | 85 | 32 |
| 2-Acetylcyclohexanone | Triton B | 30 | 24 | 2-(β -Cyanoethyl)-2-butyrylcyclopentanone | 83 | 32 |
| 2-Propionylcyclohexanone | KOH | 30 | 24 | 2-(β -Cyanoethyl)-2-acetylcyclohexanone | 67.4 | 32 |
| Acetophenone | Triton B | 25-40 | 2-4 | 2-(β -Cyanoethyl)-2-propionylcyclohexanone | 71 | 32 |
| Propiophenone | Triton B | 25-30 | 5 | $\text{C}_6\text{H}_5\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 57 | 103 |
| p-Methylacetophenone | Triton B | 25-30 | 2-4 | $\text{C}_6\text{H}_5\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_2\text{CH}_3$ | 95 | 103 |
| p-Chloroacetophenone | Triton B | 25-30 | 2-4 | $p\text{-CH}_3\text{C}_6\text{H}_4\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 90 | 103 |
| p-Bromoacetophenone | Triton B | 25-30 | 2-4 | $p\text{-ClC}_6\text{H}_4\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 90 | 103 |
| p-Methoxyacetophenone | Triton B | 25-30 | 2-4 | $p\text{-BrC}_6\text{H}_4\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 85 | 103 |
| Acetomesitylene | Triton B | 25-30 | 2-4 | $p\text{-CH}_3\text{OC}_6\text{H}_4\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 80 | 103 |
| p-Acetylbiphenyl | Triton B | 25-30 | 2-4 | $2,4,6\text{-(CH}_3)_3\text{C}_6\text{H}_2\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 30 | 103 |
| 2-Acetyl-naphthalene | Triton B | 25-30 | 2-4 | $\text{C}_6\text{H}_5\text{C}_6\text{H}_4\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 90 | 103 |
| 2-Acetyl-naphthalene | Triton B | 25-30 | 2-4 | $\text{C}_{10}\text{H}_7\text{COC}(\text{CH}_2\text{CH}_2\text{CN})_3$ | 90 | 103 |

| | | | | | | |
|--|--------------------|-------|-----|---|------|-----|
| Cyclopentanone | Triton B | 33-40 | 18 | 2,2,5,5-Tetra(β -cyanoethyl)cyclopentanone | 97 | 103 |
| Cyclohexanone | Na | 40 | — | 2,2,6,6-Tetra(β -cyanoethyl)cyclohexanone | 84 | 106 |
| Cyclohexanone | Triton B | 35-40 | 18 | 2-(β -Cyanoethyl)cyclohexanone | 10 | 103 |
| Cyclohexanone | Triton B | 35-40 | 18 | Di(β -cyanoethyl)cyclohexanone | — | 103 |
| Cyclohexanone | KOH | 35-40 | 18 | 2,2,6,6-Tetra(β -cyanoethyl)cyclohexanone | 88 | 103 |
| 4-Methylcyclohexanone | KOH | 35-40 | 18 | 2,2,6,6-Tetra(β -cyanoethyl)-4-methylcyclohexanone | 80 | 103 |
| 4-tert-Amylcyclohexanone | KOH | 35-40 | 18 | 2,2,6,6-Tetra(β -cyanoethyl)-4-tert-amylcyclohexanone | 80 | 103 |
| 4-tert-Octylcyclohexanone | KOH | 35-40 | 18 | 2,2,6,6-Tetra(β -cyanoethyl)-4-tert-octylcyclohexanone | 80 | 103 |
| 4-Cyclohexylcyclohexanone | KOH | 35-40 | 18 | 2,2,6,6-Tetra(β -cyanoethyl)-4-cyclohexylcyclohexanone | 80 | 103 |
| α -Tetralone | Triton B | 30 | 24 | 2,2-Di(β -cyanoethyl)-1-tetralone | — | 103 |
| 2-Methylcyclohexanone | Triton B | 30 | 18 | 2,2,6-Tri(β -cyanoethyl)-6-methylcyclohexanone | — | 103 |
| 2-Cyclohexenylcyclohexanone | Triton B | 30 | 2 | 2-(β -Cyanoethyl)-2-cyclohexenylcyclohexanone | 47.0 | 36 |
| 2-(β -Cyanoethyl)-2-cyclohexenylcyclohexanone | Triton B | 30 | 10 | 2,6,6-Tri(β -cyanoethyl)-2-cyclohexenylcyclohexanone | 55 | 30 |
| 2,2,5,5-Tetramethyltetrahydrofuran-3-one | Triton B | 25 | 3 | 4,4-Di(β -cyanoethyl)-2,2,5,5-tetramethyltetrahydrofuran-3-one | 71 | 103 |
| 2-Acetylfuran | Triton B | 30 | 18 | Tri(β -cyanoethyl)-2-acetylfuran | 90 | 36 |
| 2-Propionylfuran | Triton B | 30 | 24 | γ -Furoyl- γ -methylpineltonitrile | 90 | 36 |
| 2-Butyrylfuran | Triton B | 30 | 24 | γ -Furoyl- γ -ethylpineltonitrile | 68 | 36 |
| 2-Acetylthiophene | Triton B | 30 | 2 | 1,1,1-Tri(β -cyanoethyl)methyl 2-thienyl ketone | 87.7 | 36 |
| 2-Propionylthiophene | Triton B | 30 | 24 | γ -Methyl- γ -thienylpineltonitrile | 98 | 36 |
| Methyl acetacetate | NaOCH ₃ | 40 | 2 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ CH ₃ | — | 107 |
| Methyl acetacetate | Triton B | 30-40 | 1 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ CH ₃ | 50 | 103 |
| Ethyl acetacetate | Na | 60 | 6 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ C ₂ H ₅ | 25 | 110 |
| Acetoacetanilide | Na | 45-50 | 2 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ NH ₂ | 28 | 110 |
| Acetoacet- <i>o</i> -chloroanilide | Na | 40-50 | 3 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ NH ₂ Cl | — | 107 |
| Acetoacet-2,4-dichloroanilide | Na | 40-45 | 2.5 | CH ₃ COCH(CH ₂ CH ₂ CN)CO ₂ NH ₂ Cl ₂ | 70 | 107 |

TABLE XI
CYANOMETHYLATION OF NITRO COMPOUNDS AND DERIVATIVES OF MALONIC AND CYANOACETIC ACIDS

| Compound | Catalyst | Temp. °C. | Time Hr. | Product | Yield % | Reference |
|--------------------------------|----------------------------------|--------------|-------------|--|------------|-----------|
| Nitroethano | K ₂ CO ₃ | 40 | 2 | O ₂ NC(CH ₂ CH ₂ CN) ₃ | 52 | 90 |
| Nitroethano | Triton B | 30 | 18 | O ₂ NC(CH ₂ CH ₂ CN) ₃ | 45 | 37, 102 |
| Nitroethano | K ₂ CO ₃ | 40 | 1 | O ₂ NC(CH ₂) ₂ (CH ₂ CH ₂ CN) ₂ | 67 | 99 |
| Nitroethano | Triton B | 20-25 | 2 | CH ₃ CH ₂ C(CH ₂ CH ₂ CN) ₂ | — | 102 |
| 1-Nitropropano | Triton B | 40-15 | 2 | CH ₃ CH ₂ C(CH ₂ CH ₂ CN) ₂ | 20 | 102 |
| 2-Nitropropano | Triton B | 30 | 18 | (CH ₃) ₂ C(NO ₂)CH ₂ CH ₂ CN | 90 | 102 |
| 2-Nitropropano | NaOH | — | — | (CH ₃) ₂ C(NO ₂)CH ₂ CH ₂ CN | — | 100 |
| Nitrocyclohexano | NaOH | — | — | 1-Nitro-1-(β-cyanoethyl)cyclohexano | — | 100, 102 |
| α-Methoxy-β-nitropropylbenzene | NaOH | — | — | C ₆ H ₅ CH ₂ —CH(NO ₂)CH ₂ CH ₂ CN OCH ₃ CH ₂ | — | 100 |
| 0-Nitroanthrono | Triton B | 30 | 48 | 0-Nitro-9-(β-cyanoethyl)anthrono | 77 | 102 |
| Ethyl malonate | Na | 30-10 | 12 | (C ₂ H ₅ O ₂ C) ₂ C(CH ₂ CH ₂ CN) | 42 | 110 |
| Ethyl malonate | Na | 30-10 | 12 | (C ₂ H ₅ O ₂ C) ₂ C(CH ₂ CH ₂ CN) ₂ | 10 | 110 |
| Ethyl malonate | Triton B | 30 | 2 | (C ₂ H ₅ O ₂ C) ₂ C(CH ₂ CH ₂ CN) ₂ | 82.5 | 37 |
| Ethyl malonate | NaOC ₂ H ₅ | 65 | 4 | (C ₂ H ₅ O ₂ C) ₂ C(CH ₂ CH ₂ CN) ₂ | 40-45 | 120 |
| Ethyl malonate | Na | 40 | 2 | C ₂ H ₅ O ₂ CC(CN)(CH ₂ CH ₂ CN) ₂ | — | 110 |
| Ethyl cyanoacetate | Triton B | 30 | 1 | C ₂ H ₅ O ₂ CC(CN)(CH ₂ CH ₂ CN) ₂ | 97 | 37 |
| Ethyl cyanoacetate | Triton B | 30 | 1 | H ₂ NCCC(CN)(CH ₂ CH ₂ CN) ₂ | 74 | 37 |
| Cyanomalonate | Triton B | 35-40 | 1 | (H ₂ NOC) ₂ C(CH ₂ CH ₂ CN) ₂ | 13 | 37 |
| Malonanido | Triton B | 30 | 5 | (C ₂ H ₅ O ₂ C) ₂ C(C ₆ H ₅)CH ₂ CN | 79 | 37 |
| Ethyl ethylmalonate | Triton B | 30 | 6 | (C ₂ H ₅ O ₂ C) ₂ C(C ₆ H ₅)CH ₂ CN | 60 | 37 |
| Ethyl n-butylmalonate | Triton B | 30 | 2 | (C ₂ H ₅ O ₂ C) ₂ C(C ₆ H ₅)CH ₂ CN | 60 | 119 |
| Ethyl cyclopentylmalonate | NaOC ₂ H ₅ | 50 | 2 | (C ₂ H ₅ O ₂ C) ₂ C(C ₆ H ₅)CH ₂ CN | 78 | 37 |
| Ethyl benzylmalonate | Triton B | 30 | 3 | (C ₂ H ₅ O ₂ C) ₂ C(C ₆ H ₅)CH ₂ CN | — | — |

TABLE XII

CYANOETHYLATION OF ARYLACETONITRILES AND UNSATURATED NITRILES

| Compound | Catalyst | Product | Yield % | Reference |
|--------------------------------|---------------------------|---|---------|-----------|
| Benzyl cyanide | NaOC_2H_5 | $\text{C}_6\text{H}_5\text{CH}(\text{CN})\text{CH}_2\text{CH}_2\text{CN}$ | 20-33 | 47 |
| Benzyl cyanide | KOH | $\text{C}_6\text{H}_5\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 94 | 37, 121 |
| Benzyl cyanide | Na | $\text{C}_6\text{H}_5\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 78.5 | 110 |
| p-Nitrobenzyl cyanide | Triton B | $\text{O}_2\text{NC}_6\text{H}_4\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 91 | 37 |
| p-Chlorobenzyl cyanide | KOH | $\text{ClC}_6\text{H}_4\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 80 | 122 |
| p-Isopropylbenzyl cyanide | KOH | $(\text{CH}_3)_2\text{CHC}_6\text{H}_4\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 122 |
| α -Naphthylacetonitrile | KOH | $\text{C}_{10}\text{H}_7\text{C}(\text{CN})(\text{CH}_2\text{CH}_2\text{CN})_2$ | 55 | 122 |
| Crotononitrile | Triton B | α -Ethylideneglutaconitrile | 15 | 33, 123 |
| Crotononitrile | Triton B | γ -Cyano- γ -vinylpimelonitrile | 20 | 33, 123 |
| Allyl cyanide | Triton B | α -Ethylideneglutaconitrile | 11 | 33, 123 |
| Allyl cyanide | Triton B | γ -Cyano- γ -vinylpimelonitrile | 33 | 33, 123 |
| β -Methylcrotononitrile | Triton B | α -Isopropylideneglutaconitrile | — | 33, 123 |
| β -Methylcrotononitrile | Triton B | γ -Cyano- γ -isopropenylpimelonitrile | — | 33, 123 |
| Cyclohexylidenecetonitrile | Triton B | α,α -Di(2-cyanoethyl)cyclohexenylacetonitrile | 33 | 33, 123 |

TABLE XIII

MISCELLANEOUS CYANOETHYLATIONS

| Compound | Catalyst | Product | Yield % | Reference |
|---------------------------------------|--------------------------|--|---------|-----------|
| Cyclopentadiene | Triton B | 1,1,2,3,4,5-Hexa(β -cyanoethyl)cyclopentadiene | 20-30 | 124, 125 |
| Indene | Triton B | Tn(β -cyanoethyl)indene | 35 | 124, 125 |
| Fluorene | Triton B | 9,9-Di(β -cyanoethyl)fluorene | 74 | 124, 125 |
| Anthracene | Triton B | 9,9-Di(β -cyanoethyl)anthracene | 89 | 124, 125 |
| 2-Nitrofluorene | Triton B | 9,9-Di(β -cyanoethyl)-2-nitrofluorene | 70 | 124 |
| α,α -Dimethylbenzofulvene | Triton B | β -Cyanoethyl dimethylbenzofulvene | 25 | 124 |
| Chloroform | Triton B | $\text{Cl}_3\text{CCH}_2\text{CH}_2\text{CN}$ | 11 | 95 |
| Bromoform | Triton B | $\text{Br}_3\text{CCH}_2\text{CH}_2\text{CN}$ | — | 95 |
| Benzyl phenyl sulfone | Triton B | $\text{C}_6\text{H}_5\text{SO}_2\text{C}(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | 60 | 36 |
| p-Methylphenyl allyl sulfone | Triton B | $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{CH}(\text{CH}=\text{CH}_2)\text{CH}_2\text{CH}_2\text{CN}$ | — | 97 |
| p-Methylphenyl allyl sulfone | Triton B | $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{C}(\text{CH}=\text{CH}_2)(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 97 |
| Ethyl p-methylphenyl-sulfonylacetate | KOH | $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{C}(\text{CO}_2\text{C}_2\text{H}_5)(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 97 |
| Water | NaOH | $\text{NCCCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CN}$ | 45 | 39, 40 |
| Hydrogen cyanide | $\text{Ca}(\text{OH})_2$ | $\text{NCCCH}_2\text{CH}_2\text{CN}$ | 79 | 92 |
| Phenylarsine | KOH | $\text{C}_6\text{H}_5\text{As}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 85 |
| p-Aminophenylarsine | KOH | $\text{H}_2\text{NC}_6\text{H}_4\text{As}(\text{CH}_2\text{CH}_2\text{CN})_2$ | — | 85 |
| Diphenylarsine | KOH | $(\text{C}_6\text{H}_5)_2\text{AsCH}_2\text{CH}_2\text{CN}$ | — | 86 |

CHAPTER 3

THE DIELS-ALDER REACTION QUINONES AND OTHER CYCLENONES

LEWIS W. BUTZ

*Bureau of Animal Industry,
United States Department of Agriculture **

AND

ANTON W. RYTINA

Resinous Products Division, Rohm and Haas Company, Inc.

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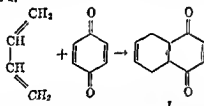
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* Present address, Chemistry Branch, Office of Naval Research.

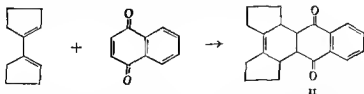
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INTRODUCTION

In addition to the dienophiles already discussed in Chapters 1 and 2 of Volume IV of *Organic Reactions*, quinones and other cyclenones react by 1,4-addition with conjugated dienes. A typical example is the reaction of butadiene with *p*-benzoquinone yielding the diketohexahydronaphthalene I.^{1,2}



By means of reactions of this type it is possible to prepare cycloolefinic ketones containing two or more fused rings. The reactions are especially useful for the preparation of fused-ring ketones containing cyclopentane rings fused to cyclohexane rings; for example, 1,4-naphthoquinone and 1,1'-bicyclopentenyl yield the pentacyclic product II.³



The diene synthesis with quinones and other cyclenones may be extended to provide a route to the preparation of fused-ring aromatic

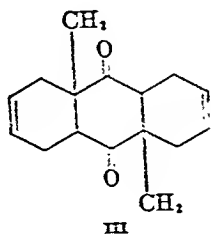
¹ Hopff and Rautenstrauch, U. S. pat. 2,262,002 [C.A., 36, 1646 (1942)].

² I. G. Farbenind. A.-G., Swiss pat. 143,253 (Chem. Zentr., 1931, I, 2937).

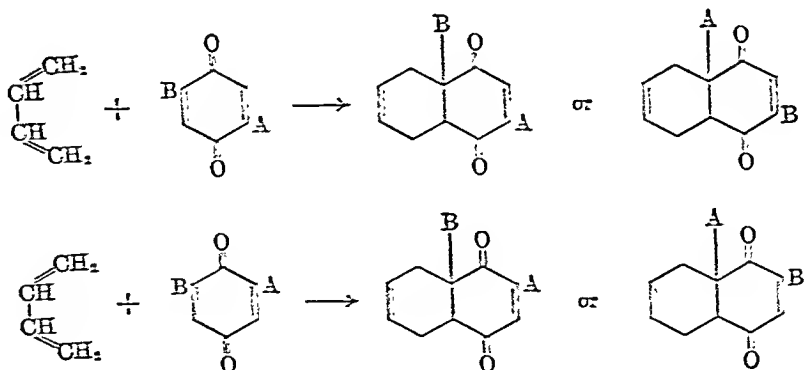
³ Barnett and Lawrence, J. Chem. Soc., 1935, 1104.

systems. The primary adducts are usually hydroaromatic systems which may be converted to aromatic compounds by dehydrogenation accompanied by enolization. Aromatization may often be effected directly by carrying out the reactions at higher temperatures in an appropriate solvent such as nitrobenzene.

It is also possible to prepare fused-ring ketones containing angular substituents. The di-adduct III from butadiene and 2,5-dimethyl-1,4-benzoquinone contains two angular methyl groups.⁴ The mono-adducts



from dienes and disubstituted *p*-benzoquinones with dissimilar substituents in the 2,5- or 2,6-positions present a special problem since they may each give rise to the two angular substituted products shown in the following general equations. It is impossible to predict the course



of additions of this type as the directing influences are imperfectly understood (see pp. 145-146).

Diene syntheses of the type described in this chapter may lead to the synthesis of compounds of steroidal structure. The reaction between 6-methoxy-1-vinyl-3,4-dihydronaphthalene and 1-methylcyclopentene-

⁴ Adler, *Arch. Chem. Mineral. Geol.*, 11B, 49 (1935) [*C.A.*, 29, 4904 (1935)].

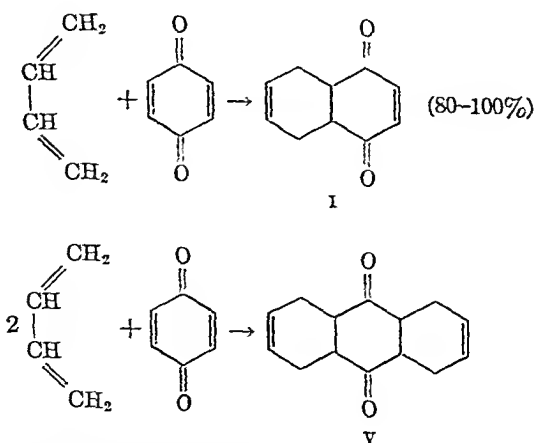
(Table VII). The reactions of these cyclenones will be discussed in the order in which the cyclenones have just been mentioned. Under each cyclenone the various dienes will be considered in order of increasing complexity.

Diels-Alder additions to cyclenones have been run in a variety of solvents or in the absence of a solvent. Most of the reactions take place at atmospheric pressure; a few are carried out in bomb tubes. With many of the *p*-benzoquinones two moles of the diene can be added to one mole of the quinone. Generally, the addition of a second mole of diene requires higher temperatures and longer reaction times. When oxidizing solvents, such as nitrobenzene, are employed the adducts are frequently dehydrogenated

Diene Additions to *p*-Benzoquinone (Table I)

Four types of dienes add to *p*-benzoquinone: simple open-chain dienes, such as butadiene and 2,3-dimethylbutadiene; monocyclic dienes, such as cyclopentadiene and 1-vinylcyclohexene; dicyclic dienes, such as 1,1'-bicyclopentenyl; and fused-ring dienes, such as 4-vinyl-1,2-dihydronaphthalene and anthracene.

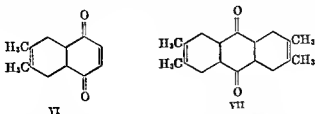
Butadiene reacts with *p*-benzoquinone in equimolar proportions to yield 1,4-diketo-1,4,4a,5,8,8a-hexahydronaphthalene (I).^{1,2,8,9} Two moles of butadiene add to one mole of *p*-benzoquinone to give the diketodecahydroanthracene (V).⁸ 2,3-Dimethylbutadiene and *p*-benzo-



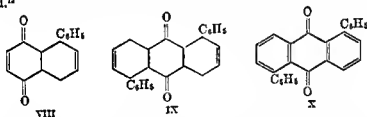
⁸ Alder and Stein, *Ann.*, 501, 247 (1933).

⁹ Alder and Stein, *Angew. Chem.*, 50, 510 (1937).

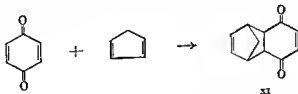
quinone react similarly to yield the mono-adduct (VI) nearly quantitatively¹ and the di-adduct (VII) in 60% yield.¹⁰ When the formation of the di-adduct is attempted in nitrobenzene at 150°, dehydrogenation to the corresponding 9,10-anthraquinone takes place.¹¹ Two moles of



1-phenylbutadiene and one mole of *p*-benzoquinone react to form a mixture of the mono- (VIII) and di-adducts (IX);¹² the structure of the di-adduct is very probably that given. At high temperature in nitrobenzene dehydrogenation takes place and X is formed in 39% yield.¹³



Equimolar quantities of cyclopentadiene and *p*-benzoquinone react in various solvents to form the expected adduct XI.^{14,15} At the melting



point (157°) the adduct decomposes into the starting materials. In boiling acetic anhydride a similar decomposition occurs, but several other products are formed from the interaction of the starting materials,

¹⁰ Morgan and Coulson, *J. Chem. Soc.*, **1931**, 2329.

¹¹ I. G. Farbenind., A.-G., Fr. pat. (addition) 39,333 [*C.A.*, **26**, 2202 (1932)].

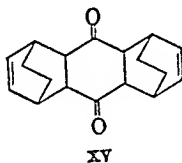
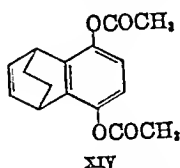
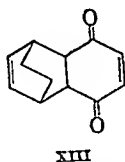
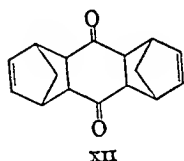
¹² Weismann, Bergmann, and Haskellberg, *J. Chem. Soc.*, **1939**, 391.

¹³ Bergmann, Haskellberg, and Bergmann, *J. Org. Chem.*, **7**, 303 (1942).

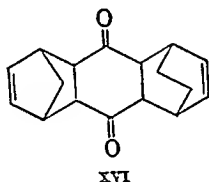
¹⁴ Albrecht, *Ann.*, **348**, 31 (1906).

¹⁵ Wassermann, *J. Chem. Soc.*, **1935**, 1511.

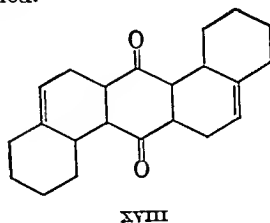
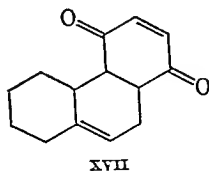
the adduct (XI), and acetic anhydride.¹⁶ Two moles of cyclopentadiene when added to one mole of *p*-benzoquinone yield XII quantitatively.^{8,14} From a reaction mixture containing three moles of 1,3-cyclohexadiene for each mole of *p*-benzoquinone, the adduct XIII may be obtained.^{2,10} This product, unlike XI, yields the quinol diacetate (XIV) with acetic anhydride.¹⁶ When a fivefold excess of 1,3-cyclohexadiene and a much longer reaction time are employed, the di-adduct XV is the product.⁸



The adduct XI, from cyclopentadiene and *p*-benzoquinone, reacts with 1,3-cyclohexadiene to yield XVI.⁸ When a 50% excess of 1-vinylcyclo-



hexene adds to *p*-benzoquinone the adduct XVII results; at higher temperature, with a 100% excess of the diene, a 10% yield of the 1,2,5,6-dibenzhydroanthraquinone XVIII is obtained.¹⁷



The reaction of 1,1'-bicyclopentenyl or 1,1'-bicyclohexenyl with *p*-benzoquinone results in the formation of the tetracyclic products XIX³ and XX^{18,3} from one mole of diene, and the heptacyclic products, XXI²⁰ and XXII,^{3,19,20} from two moles of diene.

¹⁵ Diels, Alder, and Stein, *Ber.*, **62**, 2337 (1929).

¹⁷ Cook and Lawrence, *J. Chem. Soc.*, 1938, 58.

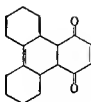
¹⁸ Bergmann, Eschinazi, and Neeman, *J. Org. Chem.*, **8**, 183 (1943).

¹⁹ Weizmann, Bergmann, and Berlin, *J. Am. Chem. Soc.*, **60**, 1331 (1938).

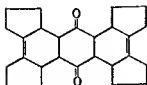
²⁰ Backer, Strating, and Huisman, *Rec. trav. chim.*, **58**, 761 (1939).



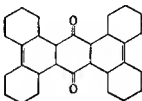
XIX



XX



XXI

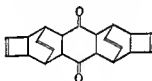


XXII

Cyclooctatetraene may be added to *p*-benzoquinone to obtain either the mono- (XXIII) or di-adduct (XXIV).²¹ 4-Vinyl-1,2-dihydronaph-

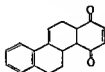


XXIII

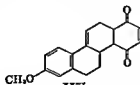


XXIV

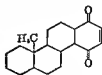
thalene adds to *p*-benzoquinone, yielding what is probably the diketohydrochrysene XXV.²² 7-Methoxy-4-vinyl-1,2-dihydronaphthalene and *p*-benzoquinone yield what is probably the methoxy analog XXVI.²³ The corresponding 4-ethynyl compound yields only an impure product.²³ The product from 4*a*-methyl-4-vinyl-1,2,4*a*,5,8,8*a*-hexahydronaphthalene and *p*-benzoquinone is a diketohydrochrysene (XXVII) in which the positions of the carbon-carbon double bonds have not been



XXV



XXVI



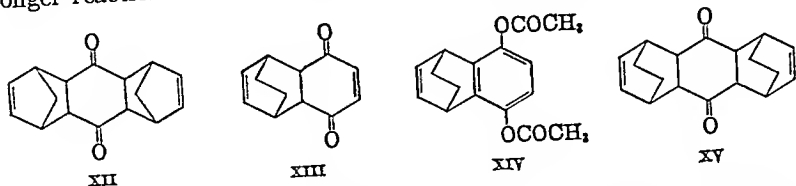
XXVII

²¹ Reppe, in *Synthetic Fiber Developments in Germany*, pp. 647, 650, 651, Textile Research Institute, Inc., New York, 1946.

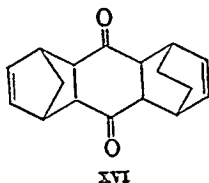
²² Dane, Höss, Bindseil, and Schmütt, *Ann.*, **532**, 42 (1937).

²³ Dane, Höss, Eder, Schmütt, and Schön, *Ann.*, **535**, 183 (1938).

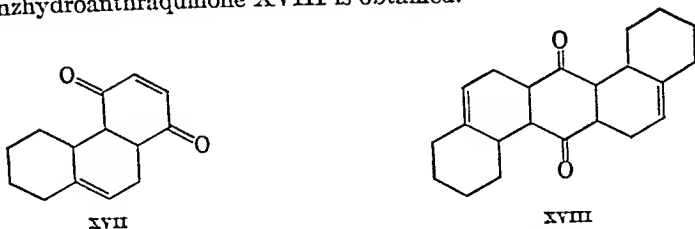
the adduct (XI), and acetic anhydride.¹⁵ Two moles of cyclopentadiene when added to one mole of *p*-benzoquinone yield XII quantitatively.^{8,14} From a reaction mixture containing three moles of 1,3-cyclohexadiene for each mole of *p*-benzoquinone, the adduct XIII may be obtained.^{2,16} This product, unlike XI, yields the quinol diacetate (XIV) with acetic anhydride.¹⁶ When a fivefold excess of 1,3-cyclohexadiene and a much longer reaction time are employed, the di-adduct XV is the product.⁸



The adduct XI, from cyclopentadiene and *p*-benzoquinone, reacts with 1,3-cyclohexadiene to yield XVI.⁸ When a 50% excess of 1-vinylcyclo-



hexene adds to *p*-benzoquinone the adduct XVII results; at higher temperature, with a 100% excess of the diene, a 10% yield of the 1,2,5,6-dibenzhydroanthraquinone XVIII is obtained.¹⁷



The reaction of 1,1'-bicyclopentenyl or 1,1'-bicyclohexenyl with *p*-benzoquinone results in the formation of the tetracyclic products XIX³ and XX^{15,2} from one mole of diene, and the heptacyclic products, XXI²⁰ and XXII,^{3,12,20} from two moles of diene.

¹⁵ Diels, Alder, and Stein, *Ber.*, **62**, 2337 (1929).

¹⁷ Cook and Lawrence, *J. Chem. Soc.*, 1938, 55.

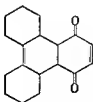
¹² Bergmann, Eschinazi, and Neeman, *J. Org. Chem.*, **8**, 183 (1943).

¹⁹ Weizmann, Bergmann, and Berlin, *J. Am. Chem. Soc.*, **60**, 1331 (1938).

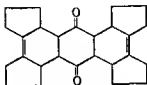
²⁰ Backer, Strating, and Huisman, *Rec. trav. chim.*, **58**, 761 (1939).



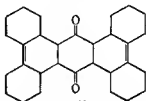
XXII



XXIII



XXIV

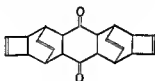


XXV

Cyclobutetetraene may be added to *p*-benzoquinone to obtain either the mono- (XXIII) or di-adduct (XXIV).²¹ 4-Vinyl-1,2-dihydronaph-

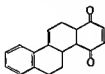


XXVI

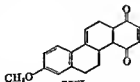


XXVII

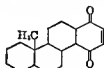
thalene adds to *p*-benzoquinone, yielding what is probably the diketohydrochrysene XXV.²² 7-Methoxy-4-vinyl-1,2-dihydronaphthalene and *p*-benzoquinone yield what is probably the methoxy analog XXVI.²³ The corresponding 4-ethynyl compound yields only an impure product.²³ The product from 4*a*-methyl-4-vinyl-1,2,4*a*,5,8,8*a*-hexahydronaphthalene and *p*-benzoquinone is a diketohydrochrysene (XXVII) in which the positions of the carbon-carbon double bonds have not been



XXVIII



XXIX



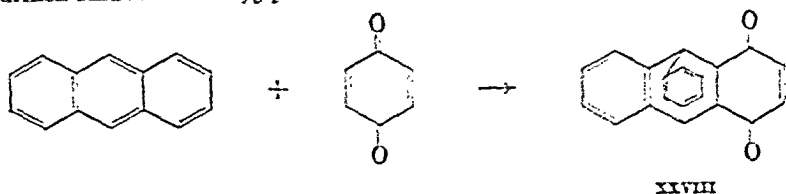
XXX

²¹ Reppe, in *Synthetic Fiber Developments in Germany*, pp. 547, 550, 551, Textile Research Institute, Inc., New York, 1946.

²² Dane, Hüss, Bindseil, and Schmitt, *Ann.*, **532**, 42 (1937).

²³ Dane, Hüss, Eder, Schmitt, and Schön, *Ann.*, **536**, 153 (1938).

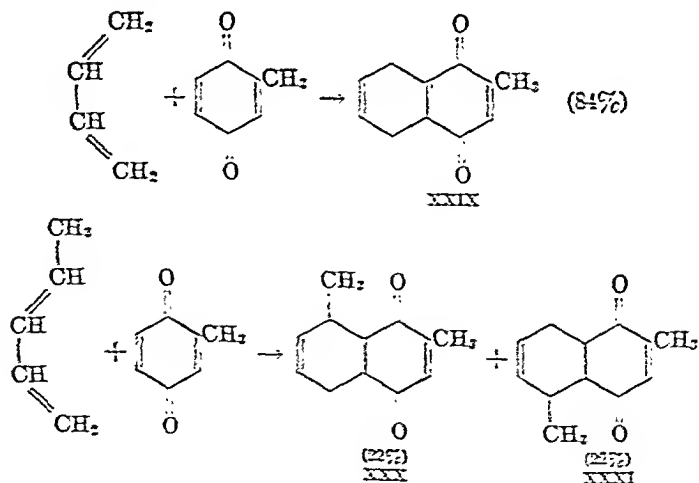
established.²¹ Equimolar quantities of anthracene and *p*-benzoquinone furnish XXVIII in 93% yield.²²



Diene Additions to Methyl-*p*-benzoquinone and Substituted Methyl-*p*-benzoquinones (Table II)

In carrying out Diels-Alder additions with methyl-*p*-benzoquinone or with substituted methyl-*p*-benzoquinones, use is made of solvents of the type employed with *p*-benzoquinone. Only simple dienes have been utilized, and, in general, greater excesses of the various dienes are used. In most reactions, temperatures below 100° are sufficient.

Excess butadiene and methyl-*p*-benzoquinone react to form the diketotetrahydronaphthalene XXIX.^{23,24} 1,3-Pentadiene and the same quinone furnish equal amounts of the structurally isomeric diketotetrahydronaphthalenes XXX and XXXI.²⁵ At temperatures below 100°,



²¹ Gaddis and Butz, *J. Am. Chem. Soc.*, 69, 1165 (1947).

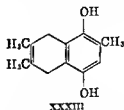
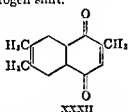
²² Clar, *Ber.*, 64, 1676 (1931).

²³ Fieser and Chang, *J. Am. Chem. Soc.*, 64, 2045 (1942).

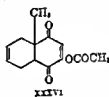
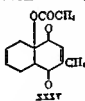
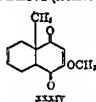
²⁴ Chuang and Han, *Ber.*, 68, 876 (1935).

²⁵ Tishler, Fieser, and Wendler, *J. Am. Chem. Soc.*, 62, 2870 (1940).

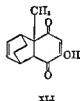
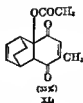
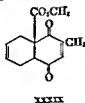
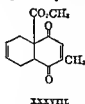
excess 2,3-dimethylbutadiene and methyl-*p*-benzoquinone form XXXII, but at 150–170° the partially aromatized product XXXIII is obtained by a hydrogen shift.²²



Butadiene,²⁰ 2,3-dimethylbutadiene,²⁰ and 1,3,5-hexatriene²¹ add in a 1:1 ratio to 2,5-dimethyl-1,4-benzoquinone to give the expected products, which are distillable oils; the comparable product from 1,3-cyclohexadiene is a solid.⁷ 2-Methoxy-5-methyl-1,4-benzoquinone gives a 75% yield of the angular methyl derivative XXXIV with butadiene,⁷ while the same diene and 2-acetoxy-5-methyl-1,4-benzoquinone give the angular acetoxy compound XXXV and the angular methyl product XXXVI (isolated as XXXVII by hydromlysis).²² 2-Carbomethoxy- and



3-carbomethoxy-5-methyl-1,4-benzoquinone give only the angular carbomethoxy products XXXVIII and XXXIX and none of the angular methyl isomers.²⁴ The reaction between 1,3-cyclohexadiene and 2-acetoxy-5-methyl-1,4-benzoquinone gives three products: an angular acetate XL, a stereoisomeric angular acetate (6%), and a trace of what is probably the angular methyl derivative XLI.²³



²⁰ Bergmann and Bergmann, *J. Org. Chem.*, **3**, 125 (1938).

²¹ Fieser and Seligman, *Ber.*, **68**, 1747 (1935).

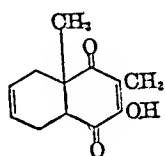
²² L. Butz, unpublished results.

²³ Butz and Butz, *J. Org. Chem.*, **8**, 497 (1943).

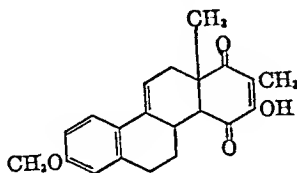
²⁴ Butz and Butz, *J. Org. Chem.*, **7**, 199 (1942).

²⁵ Nudenberg, Gaddis, and Butz, *J. Org. Chem.*, **8**, 500 (1943).

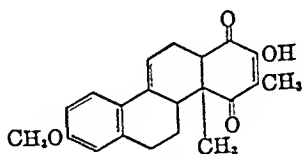
2-Hydroxy-3,5-dimethyl-1,4-benzoquinone and butadiene give the angular methyl compound XLII in 100% yield.⁵ This quinone and 7-methoxy-4-vinyl-1,2-dihydronaphthalene yield a single product which is probably one of the angular methyl derivatives XLIII or XLIIIA.⁵



XLII



XLIII



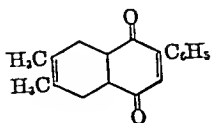
XLIIIA

Tetramethyl-*p*-benzoquinone and 1,3,5-hexatriene react at temperatures above 150°. The reaction is not of the Diels-Alder type; instead the quinone is reduced to the hydroquinone.²⁵

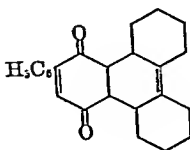
Diene Additions to Substituted *p*-Benzoquinones Other than Methyl-*p*-benzoquinones (Table III)

Diene additions to these more complexly substituted *p*-benzoquinones are generally carried out in aromatic solvents such as benzene and xylene. The temperatures required are about the same as with the methyl-*p*-benzoquinones.

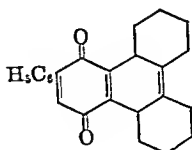
Excess 2,3-dimethylbutadiene (5.5 moles) reacts with 1 mole of phenyl-*p*-benzoquinone to yield a single product XLIV in 82% yield.²⁹ 1,1'-Bicyclohexenyl and phenyl-*p*-benzoquinone in the absence of a solvent give what is considered to be the expected adduct XLV, while in nitrobenzene the quinone XLVI is formed.¹⁹ 2,5-Diphenyl-1,4-benzoquinone



XLIV



XLV

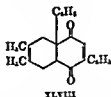
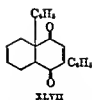


XLVI

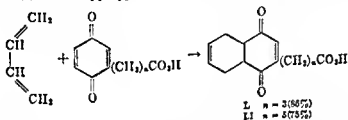
reacts with butadiene, 2,3-dimethylbutadiene, and 1-phenylbutadiene to yield what are apparently the angular adducts XLVII, XLVIII, and XLIX in 77%, 79%, and 89% yields, respectively.²⁸

²⁸ L. Butz and Gaddis, unpublished results.

²⁹ Allen, Bell, Clark, and Jones, *J. Am. Chem. Soc.*, **66**, 1617 (1944).



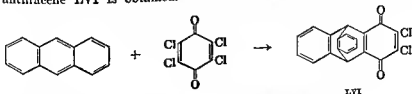
ω -Carboxypropyl- and ω -carboxyamyl-*p*-benzoquinone react with butadiene to form the expected products L and LI.²⁷ The most striking feature of these reactions is the large diene:quinone ratio employed; 30:1 with the carboxypropyl- and 10:1 with the carboxyamyl-quinone.



Chloro-*p*-benzoquinone reacts with 2,3-dimethylbutadiene²⁸ and with 2-chlorobutadiene,¹ yielding the expected products LII and LIII. 2,3-Dichloro-1,4-benzoquinone reacts similarly with butadiene and with 2,3-dimethylbutadiene, yielding LIV and LV.²⁸ Diene additions to



tetrachloro-*p*-benzoquinone are accompanied by the loss of a molecule of chlorine and lead to dichloro adducts. Tetrachloro-*p*-benzoquinone and cyclopentadiene give a 1:1 adduct of unknown structure;^{14,29} with anthracene LVI is obtained.²⁵ 10-Methylene-9-anthrone and tetra-

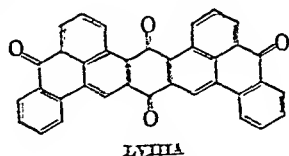
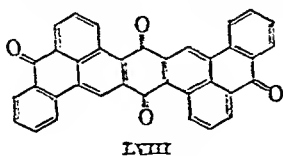
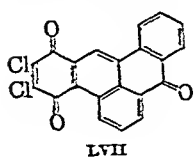


²⁷ Fieser, Gates, and Kilmer, *J. Am. Chem. Soc.*, **62**, 2906 (1940).

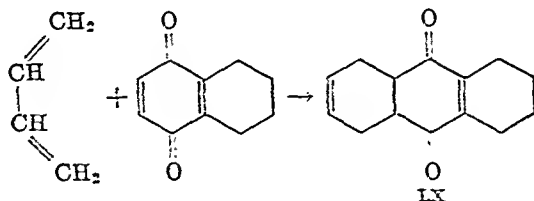
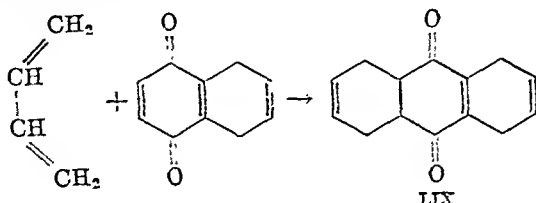
²⁸ I.G. Farbenind. A.-G., Fr. pat. 677,296 [*C.A.*, **24**, 3118 (1930)].

²⁹ Wassermann, Fr. pat. 833,454 [*C.A.*, **33**, 7813 (1939)].

chloro-*p*-benzoquinone in xylene give the dichloro compound LVII. In nitrobenzene two moles of diene add, and the adduct LVIII or LVIIIA is halogen free.⁴⁰ 5,8-Dihydro-1,4-naphthoquinone and 5,6,7,8-tetra-



hydro-1,4-naphthoquinone react with butadiene in the expected manner, yielding LIX and LX.^{33, 41}



Diene Additions to *o*-Quinones (Table IV)

Relatively few *o*-quinones have been utilized in Diels-Alder additions. In all the reactions for which data are available, the ratio of diene to quinone employed has been quite large (2.5:1 to 34:1). Most of these reactions were carried out in ethanol or in chloroform.

o-Benzoquinone and cyclopentadiene give a 1:1 adduct of unknown constitution while tetramethyl-*o*-benzoquinone and cyclopentadiene react to form the *endomethylene* adduct LXI in 63% yield.⁴² 2,3-Dimethylbutadiene and 3,7-dimethyl-1,2-naphthoquinone yield the angular methyl derivative LXII.⁴³

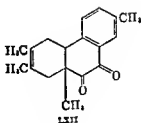
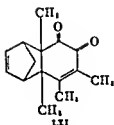
⁴⁰ Clar, *Ber.*, 69, 1686 (1936).

⁴¹ I.G. Farbenind. A.-G., Brit. pat. 327,128 [*C.A.*, 24, 5045 (1930)].

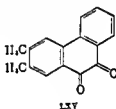
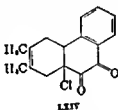
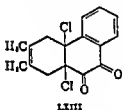
⁴² Smith and Har, *J. Am. Chem. Soc.*, 53, 229 (1935).

⁴³ Fieser and Seligman, *J. Am. Chem. Soc.*, 56, 2099 (1934).

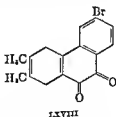
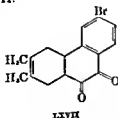
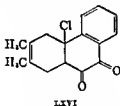
⁴⁴ Fieser and Dunn, *J. Am. Chem. Soc.*, 59, 1021 (1937).



Several chloro- and bromo-1,2-naphthoquinones participate in Diels-Alder additions. With the exception of LXIII, the product from 2,3-dimethylbutadiene and 3,4-dichloro-1,2-naphthoquinone,⁴⁸ all the adducts are unstable. The adduct LXIV from 2,3-dimethylbutadiene and 3-chloro-1,2-naphthoquinone decomposes in a few hours when kept in a vacuum. When warmed with ethanolic sodium acetate it yields 2,3-dimethyl-9,10-phenanthraquinone (LXV) quantitatively.⁴⁸ The adduct



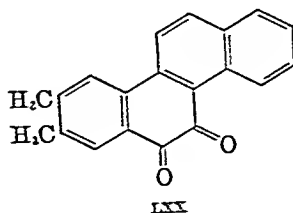
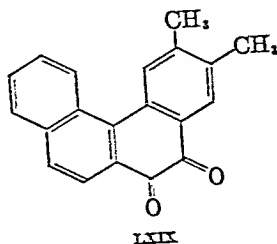
LXVI cannot be isolated from the reaction of 4-chloro-1,2-naphthoquinone and 2,3-dimethylbutadiene, but the reaction mixture yields 2,3-dimethyl-9,10-phenanthraquinone (LXV) on standing in air.⁴⁸ 6-Bromo-1,2-naphthoquinone and 2,3-dimethylbutadiene yield the nearly pure adduct LXVII which undergoes dehydrogenation on recrystallization to yield LXVIII.⁴⁹



1,2-Phenanthraquinone with 2,3-dimethylbutadiene yields the tetracyclic product LXIX, which is also obtained from the same diene and

⁴⁸ Fieser and Dunn, *J. Am. Chem. Soc.*, **59**, 1016 (1937).

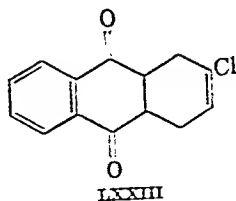
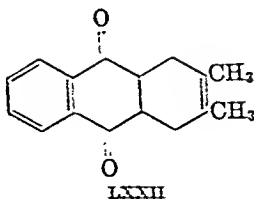
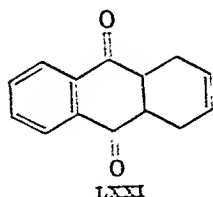
3-bromo-1,2-phenanthraquinone.⁴⁶ 2-Bromo-3,4-phenanthraquinone and 2,3-dimethylbutadiene yield an oil which on oxidation with chromic acid gives the quinone LXX in 90% yield.⁴⁵



Diene Additions to 1,4-Naphthoquinone (Table V)

A large variety of dienes add to 1,4-naphthoquinone. The addition is limited to the double bond in the 2,3-position, and as a result only 1:1 adducts have been reported.

Butadiene adds to 1,4-naphthoquinone to yield the diketohydroanthracene (LXXI).^{42, 47, 48} 2,3-Dimethylbutadiene in ethanol or in the absence of a solvent gives the expected product LXXII; in nitrobenzene the 9,10-anthraquinone is obtained.⁴¹ 1-Chlorobutadiene does not react with 1,4-naphthoquinone,⁴² but 2-chlorobutadiene yields LXXIII although considerable amounts of starting materials are recovered.⁵⁰ 2-Bromobutadiene and 1,4-naphthoquinone react in similar fashion.⁵¹



The 3-chloro- derivatives of pentadiene, 1,3-hexadiene, 1,3-octadiene, and 1,3-hendecadiene yield 9,10-anthraquinones after aeration of the adducts.⁴² 2,3-Dimethoxybutadiene and 1,4-naphthoquinone react, and

⁴¹ Fieser and Dunn, *J. Am. Chem. Soc.*, **59**, 1024 (1937).

⁴² I.G. Farbenind. A.-G., Swiss pat. 143,259 (*Chem. Zentr.*, 1931, I, 2937).

⁴³ Diels and Alder, *Ann.*, **460**, 110 (1925).

⁴⁴ Coffman and Carothers, *J. Am. Chem. Soc.*, **55**, 2043 (1933); Berchet and Carothers *ibid.*, **55**, 2004 (1933).

⁴⁵ Carothers, Williams, Collins, and Kirby, *J. Am. Chem. Soc.*, **53**, 4206 (1931).¹

⁴⁶ Carothers, Collins, and Kirby, *J. Am. Chem. Soc.*, **55**, 785 (1933).

⁴⁷ Jacobson and Carothers, *J. Am. Chem. Soc.*, **55**, 1526 (1933).

the adduct, which has not been isolated, yields 2,3-dimethoxy-9,10-anthraquinone when treated with sodium hypochlorite.¹³

Cyclopentadiene and 1,3-cyclohexadiene add to 1,4-naphthoquinone giving LXXIV¹⁴ and LXXV.¹⁵ The *endomethylene* adduct LXXIV is unstable and gives 1,4-naphthohydroquinone diacetate with acetic anhydride. Air and ethanolic alkali dehydrogenate the *endoethylene* adduct LXXV to LXXVI, which decomposes to ethylene and anthraquinone at 150°.¹⁶ α -Chlorovinylcyclohexene and 1,4-naphthoquinone



LXXIV

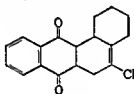


LXXV

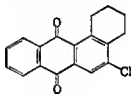


LXXVI

yield LXXVII, which can be partially dehydrogenated to yield LXXVIII.¹⁶

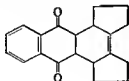


LXXVII

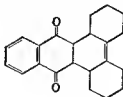


LXXVIII

1,1'-Bicyclopentenyl and 1,1'-bicyclohexenyl react with 1,4-naphthoquinone yielding the pentacyclic products II¹⁷ and LXXIX.¹⁸ Cyclo-



II



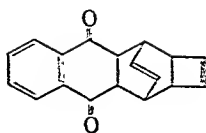
LXXIX

octatetraene and 7,8-dichlorobicyclo-[0.4.2]-octa-2,4-diene react with 1,4-naphthoquinone yielding the complex adducts LXXX and LXXXI.²¹ 10-Methylene-9-anthrone and 1,4-naphthoquinone give LXXXII.^{22,23}

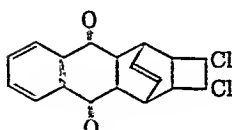
¹³ Johnson, Jobling, and Bodamer, *J. Am. Chem. Soc.*, **63**, 131 (1941).

¹⁴ Carothers and Coffman, *J. Am. Chem. Soc.*, **54**, 4071 (1932).

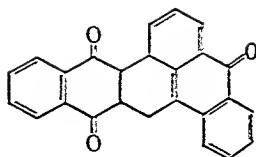
¹⁵ I.G. Farbenind. A.-G., Ger. pat. 591,496 [*C.A.*, **23**, 2366 (1934)].



LXXXVI



LXXXVII



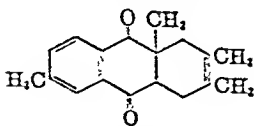
LXXXVIII

Tetraphenylcyclopentadienone (cyclone) and 3,4-(1,8-naphthylene)-2,5-diphenylcyclopentadienone do not react with 1,4-naphthoquinone.⁵⁵

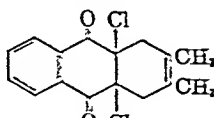
Diene Additions to Substituted 1,4-Naphthoquinones (Table VI)

Many substituted 1,4-naphthoquinones have been employed in Diels-Alder additions. Temperatures necessary for reaction are usually above 100°, and in all reactions solvents are employed.

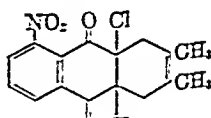
2,6-Dimethyl-1,4-naphthoquinone and 2,3-dimethylbutadiene give a solid adduct LXXXIX; the reaction between 2,3-dimethyl-1,4-naphthoquinone and the same diene proceeds more slowly and yields an impure liquid.⁵⁶ 2-Chloro-1,4-naphthoquinone and butadiene give a 9,10-diketo-1,4-dihydroanthracene; with 2-methylbutadiene a 9,10-anthraquinone is the product.⁵⁷ 2,3-Dimethylbutadiene reacts with 2,3-dichloro-1,4-naphthoquinone and with 2,3-dichloro-5-nitro-1,4-naphthoquinone yielding LXXXIV and LXXXV.⁵⁷



LXXXIX

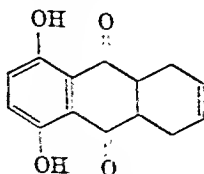


LXXXIV

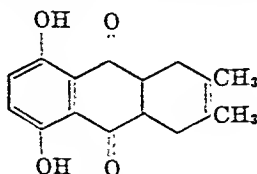


LXXXV

That 2-hydroxy-1,4-naphthoquinone reacts with 2,3-dimethylbutadiene is shown by the isolation of 2,3-dimethylantraquinone after suitable treatment of the reaction product.⁵⁸ 5,8-Dihydroxy-1,4-naphthoquinone reacts with butadiene and 2,3-dimethylbutadiene yielding LXXXVI and LXXXVII.⁵⁷ 5,8-Diacetoxy-, 5,6,8-trihydroxy-, and



LXXXVI

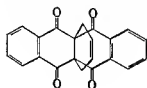


LXXXVII

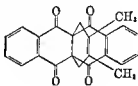
⁵⁵ Arbusov, Abramov, and Deryazov, *J. Gen. Chem. U.S.S.R.*, 9, 1559 (1939) [*C.A.*, 34, 2839 (1940)].

⁵⁷ I.G. Farbermand, A.-G., Brit. pat. 339,375 [*C.A.*, 24, 2757 (1930)].

5,6,8-triacetoxy-1,4-naphthoquinone react with the simpler dienes giving the expected products (Table VI, p. 186). 5,6,11,12-Naphtbacenedi-quinone reacts with butadiene and with 2,3-dimethylbutadiene to yield the complex adducts LXXXVIII and LXXXIX.⁴⁸



LXXXVIII

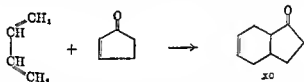


LXXXIX

Diene Additions to Cyclenones Other than Quinones (Table VII)

Many conjugated cyclenones have been used in Diels-Alder additions to yield a variety of fused-ring ketones or diketones. Generally the cyclenones require temperatures above 100° and longer periods of heating than the quinones.

Cyclopenten-3-one and butadiene react slowly yielding the bicyclic adduct XC in addition to some resinous material.⁴⁹ 1-Methylcyclo-



XC

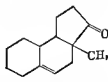
penten-5-one and 2,3-dimethylbutadiene give the angular methyl product XCI in 52% yield.⁴⁹ This cyclenone also reacts with 1-vinylcyclohexene giving a 75% yield of an angular methyl derivative formulated as XCII or XCIIA.⁴⁹ 4a-Methyl-4-vinyl-1,2,4a,5,8,8a-hexahydronaph-



XCI



XCII



XCIIA

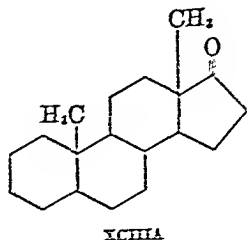
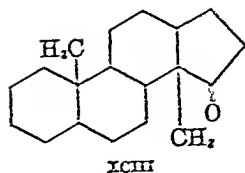
thalene and 1-methylcyclopenten-5-one give a product whose structure has not been established but whose elementary composition corresponds

⁴⁸ Fieser and Dunn, *J. Am. Chem. Soc.*, **58**, 1054 (1936).

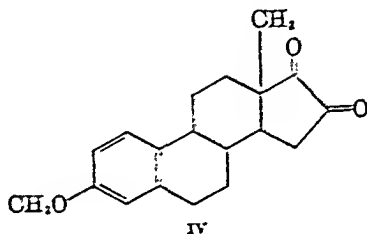
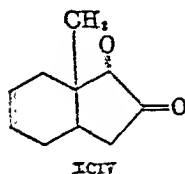
⁴⁹ Dane and Eder, *Ann.*, **539**, 207 (1939).

⁵⁰ Bockemüller, U. S. pat. 2,179,809 [*C.A.*, **34**, 1823 (1940)].

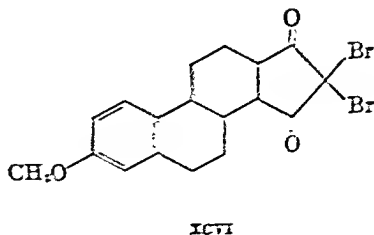
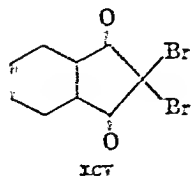
to that of XCIII or XCIIIA.⁵¹ 1-Methylcyclopentene-4,5-dione and



butadiene yield the angular methyl product XCIV,⁵² while this cyclenone and 6-methoxy-1-vinyl-3,4-dihydronaphthalene give a 15,16- or a 16,17-diketosteroid which has been formulated as IV.⁵⁶ The structure of this product is uncertain (see p. 139). 4,4-Dibromocyclopentene-3,5-dione



and butadiene give XCV in unspecified yield, while the same dione and 6-methoxy-1-vinyl-3,4-dihydronaphthalene give a 16,16-dibromo-15,17-diketosteroid XCVI.⁵⁹



Butadiene and 2,3-dimethylbutadiene react with cyclohexen-3-one giving the octalones XCVII and XCVIII in 11 and 20% yields.⁶² Combination of this cyclenone with 1-methyl-2-vinylcyclohexene followed

⁵¹ Gaddis and Butz, *J. Am. Chem. Soc.*, **69**, 1933 (1947).

⁵² Dane, Schmitt, and Rautenstrauch, *Ann.*, **532**, 29 (1937); Dane, U. S. pat. 2,230,223 [*CA.*, **35**, 3337 (1941)].

⁵⁹ Bartlett and Woods, *J. Am. Chem. Soc.*, **62**, 2933 (1940).

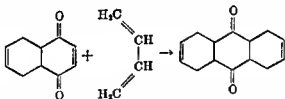
by treatment with 2,4-dinitrophenylhydrazine yields what may be the 2,4-dinitrophenylhydrazone of XCIX or XCIXA.⁴⁴ Cyclohexadiene



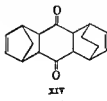
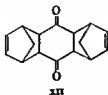
fails to react with cyclohept-3-one.⁴⁵ Butadiene and 1,3,5-hexatriene do not react with 1-methylcyclohept-3-one.⁴⁶ However, butadiene and 1-methylcyclohexen-6-one react to form C.⁴⁷



The 1:1 adducts obtained from *p*-benzoquinone and a variety of dienes (discussed on pages 140-143) can add a second mole of diene. A typical example is the diketotetrahydronaphthalene (from *p*-benzoquinone and butadiene) which reacts with butadiene,⁴⁸ 2,3-dimethylbutadiene,^{49,50} cyclopentadiene,⁵¹ and 1,3-cyclohexadiene⁵² to yield the expected adducts. The 1:1 adduct from *p*-benzoquinone and cyclo-



pentadiene (XI) reacts with cyclopentadiene and 1,3-cyclohexadiene giving XII⁵³ and XIV.⁵⁴ The 1:1 adduct (XIX) from *p*-benzoquinone



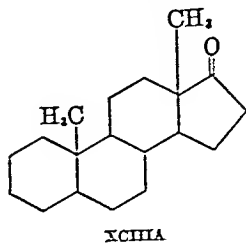
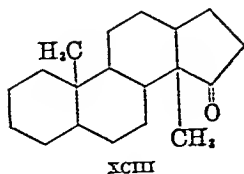
⁴⁴ Meggy and Robinson, *Nature*, **140**, 282 (1937).

⁴⁵ Whitmore and Pedlow, *J. Am. Chem. Soc.*, **63**, 758 (1941).

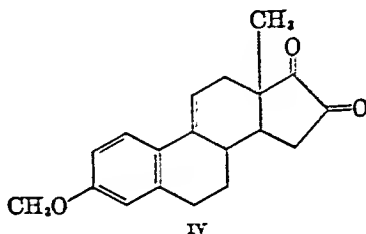
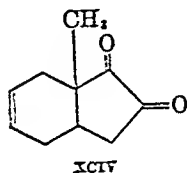
⁴⁶ Robinson and Walker, *J. Chem. Soc.*, **1935**, 1530.

⁴⁷ Nudenberg and Buts, *J. Am. Chem. Soc.*, **63**, 1436 (1943).

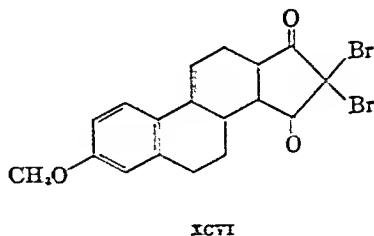
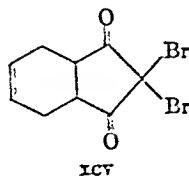
to that of XCIII or XCIIIA.⁴¹ 1-Methylcyclopentene-4,5-dione and



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Butadiene and 2,3-dimethylbutadiene react with cyclohexen-3-one giving the octalones XCVII and XCVIII in 11 and 20% yields.⁴⁴ Combination of this cyclenone with 1-methyl-2-vinylcyclohexene followed

⁴¹ Gaddis and Butz, *J. Am. Chem. Soc.*, **69**, 1203 (1947).

⁴² Dane, Schmitt, and Rautenstrauch, *Ann.*, **532**, 29 (1937); Dane, U. S. pat. 2,230,203 [C.A., **35**, 2037 (1941)].

⁴³ Bartlett and Woods, *J. Am. Chem. Soc.*, **62**, 2933 (1940).

by treatment with 2,4-dinitrophenylhydrazine yields what may be the 2,4-dinitrophenylhydrazone of XCIX or XCIXA.⁴⁴ Cyclohexadiene



XCVII



XCVIII



XCIX



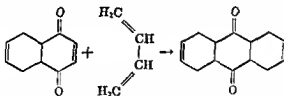
XCIXA

fails to react with cyclohexen-3-one.⁴⁵ Butadiene and 1,3,5-hexatriene do not react with 1-methylcyclohexen-3-one.⁴⁶ However, butadiene and 1-methylcyclohexen-6-one react to form C.⁴⁷



C

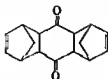
The 1:1 adducts obtained from *p*-benzoquinone and a variety of dienes (discussed on pages 140-143) can add a second mole of diene. A typical example is the diketotetrahydronaphthalene (from *p*-benzoquinone and butadiene) which reacts with butadiene,⁴⁸ 2,3-dimethylbutadiene,^{49,51} cyclopentadiene,⁸ and 1,3-cyclohexadiene⁹ to yield the expected adducts. The 1:1 adduct from *p*-benzoquinone and cyclo-



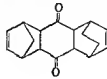
pentadiene (XI) reacts with cyclopentadiene and 1,3-cyclohexadiene giving XII⁵² and XIV.⁸ The 1:1 adduct (XIX) from *p*-benzoquinone



XI



XII



XIV

⁴⁴ Meggy and Robinson, *Nature*, 140, 282 (1937).

⁴⁵ Whitmore and Pedlow, *J. Am. Chem. Soc.*, 63, 758 (1941).

⁴⁶ Robinson and Walker, *J. Chem. Soc.*, 1933, 1530.

⁴⁷ Nudenberg and Buts, *J. Am. Chem. Soc.*, 65, 1436 (1943).

of temperatures between 90° and 110° , a reaction time of twenty-four hours, and, as the solvent, benzene, ethanol, or excess diene.

The addition of 5,6,8-triacetoxy-1,4-naphthoquinone to 2,3-dimethylbutadiene in ethanol precisely exemplifies the conditions taken as standard. Naphthoquinones with fewer substituents in the benzenoid ring react completely within much shorter periods.⁴⁵ The most reactive of the series (Table VI), the 5-hydroxy derivative, gave 95% of adduct in twenty minutes.

Some quinone additions require longer periods at 100° . 2,5-Dimethyl-1,4-benzoquinone in ethanol gave a higher yield after seventy-two hours than after twenty-seven. The yield was still higher at seventy-two hours in benzene. Such a difference in favor of benzene as against ethanol has not been observed in any other reaction.

The standard conditions are adequate for the addition of some quinones with a methyl group at the reacting double bond. An example is 2-methyl-8-hydroxy-1,4-naphthoquinone. With the variation of dioxane as solvent, 2-hydroxy-3,5-dimethyl-1,4-benzoquinone reacts under these conditions.

For the preparation of 2-cyclene-1,4-diones without substituents at carbons 2 or 3, a lower temperature must be used and an excess of diene avoided. A temperature of $35-40^{\circ}$ in organic solvents or in aqueous emulsion is suitable (Table I). At higher temperatures the cyclenedione reacts with another mole of diene. Thus the diketodiethanohydroanthracene XV, p. 142, is obtained in theoretical yield by refluxing *p*-benzoquinone and cyclohexadiene ($80-85^{\circ}$) for twenty-four hours.

Monoketones definitely require a higher temperature. Methylcyclopenten-5-one and vinylcyclohexene at 170° for sixteen hours give only 52% of the adduct; at 205° for twenty-four hours the yield is 75%. An excess of the ketone (Table VII) may be essential.

The conditions taken as standard are probably as vigorous as can be tolerated in the preparation of 2-cyclene-1,4-diones which lack an angular substituent at carbon 5 or the other angular carbon atom. Otherwise, rearrangement to a 1,4-hydroquinone will take place.

A longer period (fifty hours) was used for additions to methylcyclopenten-4,5-dione in dioxane (Table VII). The group $-\text{COCR}=\text{CHCO}-$, where R is methyl, ω -carboxypropyl, or ω -carboxyamyl in cyclohexenediones which are not quinones, does not react with butadiene in benzene at 70° within six hours. In the preparation of some diketohexahydronaphthalenes containing this group (Tables II and III) it is standard practice to heat in the presence of an excess of diene. The $-\text{COC}(\text{C}_6\text{H}_5)=\text{CHCO}-$ group in these cyclohexenediones does not react in one hour at 100° when the compound is dissolved in 2,3-di-

methylbutadiene, but this group in 2,5-diphenyl-1,4-benzoquinone does react with 2,3-dimethylbutadiene in boiling ethanol (six days, 79%).

The selection of solvent is important with certain unstable quinones. *It is sometimes necessary to keep all the quinone dissolved during the reaction to prevent decomposition of suspended particles which initiates decomposition throughout the mixture.* For this reason ethanol may be preferred to benzene. The addition of a few drops of acetic acid to the ethanol has been found advisable.⁶⁷ However, additions of 3- and 4-halo-1,2-naphthoquinones cannot be carried out successfully in ethanol.

There is evidence that *p*-benzoquinone and cyclopentadiene react more rapidly in certain solvents than in others (fast in benzene or ethanol, slow in carbon bisulfide, carbon tetrachloride, or *n*-hexane) (Table I). This reaction proceeds five times as fast, for a given activation energy, in nitrobenzene as it does in benzene.⁶⁸ No application of such information to preparative work seems yet to have been made.

No careful study of the relative reactivities of various dienes is available. Some of the data suggest that 1-substituted and 1,4-disubstituted butadienes react more slowly than others. For the addition of toluquinone to pentadiene forty hours was allowed, as compared with six for the addition of butadiene (Table II).

Preparations from unstable dienes can be carried out to advantage in aqueous dispersion. Effective withdrawal of heat of reaction is attained in the presence of the water. Polymerization inhibitors, such as copper and its salts, phenols, or amines, may also be added.

Occasionally the determination of ultraviolet absorption spectra may be useful in distinguishing a hydroquinone from a cyclenedione. Curves for typical hydroquinones⁶⁴ and cyclenediones⁶⁵ are available for comparison. The spectra may be valuable in detecting products of side reaction as well as rearrangement products. Although 1,6-addition of a 1,3-diene to a *p*-quinone to give a 1,4-hydroquinone monoether does not appear to be an interfering reaction in most quinone-diene syntheses, highly hindered quinones might react in this way.⁶⁶ Diisopropenylacetylene reacts with 1 mole of tetrachloro-*p*-benzoquinone to give a crystalline compound whose ultraviolet absorption is almost identical with that of tetrachlorohydroquinone.⁶⁷ The structure of the adduct from cyclopentadiene and tetrachloro-*p*-benzoquinone has never been demonstrated.⁶⁷

⁶⁴ Hinshelwood, *J. Chem. Soc.*, 1938, 236.

⁶⁵ Schjaneberg, *Swensk Kem. Tidn.*, 62, 185 (1940) [*C.A.*, 34, 7742 (1940)].

⁶⁶ Bastron, Davis, and Buts, *J. Org. Chem.*, 8, 515 (1943).

⁶⁷ Criegee, *Ber.*, 69, 2753 (1936).

⁶⁸ Buts, Gaddin, and Buts, *J. Am. Chem. Soc.*, 69, 924 (1947).

Addition of a Diene to *p*-Benzoquinone; Preparation of 6-Chloro-1,4-diketo-1,4,4 α ,5,8,8 α -hexahydronaphthalene.¹ To an emulsion of 112.5 parts of 2-chlorobutadiene in 500 parts of water containing 10 parts of an emulsifier made from 40 moles of ethylene oxide and 1 mole of castor oil is added 137.5 parts of *p*-benzoquinone. The mixture is stirred in the dark at 40° for twelve hours, cooled to 4°, and filtered. The adduct, which melts at 95° and is obtained in a 95% yield, is extraordinarily sensitive to light.

Addition of a Diene to a Substituted *p*-Benzoquinone; Preparation of 5,7,8-Triketo-6,10-dimethyl-2-octalin (XLII, p. 146).^{5,22} Half a gram of 2-hydroxy-3,5-dimethyl-1,4-benzoquinone, 4 ml. of butadiene, and 4 ml. of dioxane are heated at 110° for twenty hours in a sealed tube. The original yellowish red color changes to a bright yellow. After evaporation of the dioxane in vacuum, the residue crystallizes completely. Recrystallization from ether-petroleum ether gives a theoretical yield of colorless trione, m.p. 120°. Purification by high-vacuum sublimation at 110° is also possible. Similarly prepared triones which are not so easily purified can be obtained from the reaction mixtures by diluting with ether, extracting with aqueous sodium hydroxide, precipitating the trione from the water solutions of its sodium salt with dilute sulfuric acid, extracting with ether, and evaporating the ether after washing and drying.

Addition of a Diene to 1,4-Naphthoquinone; Preparation of 6,7-Dimethyl-9,10-diketo-5,8,8 α ,9,10,10 α -hexahydroanthracene and 2,3-Dimethylantraquinone. Excellent directions for the addition of 2,3-dimethylbutadiene to 1,4-naphthoquinone and subsequent dehydrogenation of the 1:1 adduct to 2,3-dimethylantraquinone have been published in *Organic Syntheses*.⁵³

Addition of a Diene to a 1,2-Naphthoquinone; Preparation of 10 α -Chloro-2,3-dimethyl-9,10-diketo-1,4,4 α ,9,10,10 α -hexahydro-9,10-phenanthraquinone (LXIV, p. 149) and 2,3-Dimethyl-9,10-phenanthraquinone (LXV, p. 149).⁴⁵ A mixture of 4 g. of 3-chloro-1,2-naphthoquinone, 8 ml. of 2,3-dimethylbutadiene, and 40 ml. of purified chloroform (shaken with concentrated sulfuric acid, then washed with water, dried, and distilled) is sealed in a tube and heated in a steam bath with exclusion of light. The tube is shaken vigorously until all solid material has dissolved, for it is generally found that solid particles of a quinone tend to suffer decomposition and initiate the destruction of material in solution. The red color of the solution soon begins to fade and in fifty minutes has changed to yellow. After one hour the solution is cooled and shaken with Norit for ten minutes at room temperature, and the

⁵³ Allen and Bell, *Org. Syntheses*, 22, 37 (1942).

solvent is distilled from the filtered solution in vacuum, the temperature being kept below 60°. The resulting viscous oil can be preserved for some time as such or in ethereal solution without decomposing. Crystalline material is obtained by cooling an ethereal solution in a bath of solid carbon dioxide and adding petroleum ether, and with seed available the crystalline compound is obtained easily. Recrystallized from ether-petroleum ether, the adduct forms glistening, lemon-yellow needles, m.p. 87–88°; yield, 4 g. (70%).

The pure diketone adduct, suspended in ethanol or ether, when shaken with air, soon changes to an orange powder, which is crystallized from glacial acetic acid to give orange plates of 2,3-dimethyl-9,10-phenanthraquinone, m.p. 242–243° (cor.); yield, 87%. Warming the oily or crystalline diketone adduct with ethanolic sodium acetate solution gives 2,3-dimethyl-9,10-phenanthraquinone; yield, 100%.

To obtain satisfactory results in this diene addition, it is essential to prepare the quinone in a high state of purity and to employ pure chloroform or tetrachloroethane. Ethanol has a deleterious effect; even the small quantity present in commercial chloroform brings about extensive decomposition.

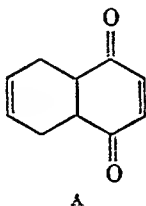
Addition of a Diene to a 1,2-Phenanthraquinone; Preparation of 6,7-Dimethyl-3,4-benzo-9,10-phenanthraquinone (LXIX, p. 150).⁴⁴ One gram of 3-bromo-1,2-phenanthraquinone and 6 ml. of 2,3-dimethylbutadiene are heated in 70 ml. of purified chloroform (see the preceding preparation) in a steam bath for three hours. The oil remaining after removal of the solvents is treated in 6 ml. of glacial acetic acid with 2 g. of chromic anhydride in 20 ml. of 80% acetic acid with gentle warming. By gradually adding water to the solution and scratching, 6,7-dimethyl-3,4-benzo-9,10-phenanthraquinone is caused to separate in a microcrystalline condition; yield, 79%. Recrystallization from ethanol yields lustrous, fiery-red plates, m.p. 194–195°.

SURVEY OF DIELS-ALDER DIENE-CYCLENONE ADDITIONS

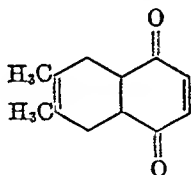
In the tables are listed examples of diene additions to cyclenones which have been reported through 1946. The list may not be complete, as the reaction is often used merely to show the presence of a conjugated diene and such examples may have escaped notice.

Many of the adducts formed in these reactions are derivatives of complex polycyclic systems, and their structural formulas are so bulky that their use would expand the tables unduly. Their names also are cumbersome and have the additional disadvantage that most chemists are not familiar with them. We have therefore been forced to adopt the

following expedient: Before each table is listed a group of structural formulas with their corresponding symbols. For example, 1,4-diketo-1,4,4a,5,8,8a-hexahydronaphthalene has the symbol A.



When this diketohexahydronaphthalene or its substitution product is formed and its structure established, the symbol A is used in the column under "Products." Although A actually refers only to the 1:1 adduct from butadiene and *p*-benzoquinone, the reader can easily work out the positions of the substituents when other dienes or *p*-benzoquinones are used and the reaction follows a normal course. Thus, the product from 2,3-dimethylbutadiene and *p*-benzoquinone has the symbol A which here denotes the 6,7-dimethyl derivative shown below.

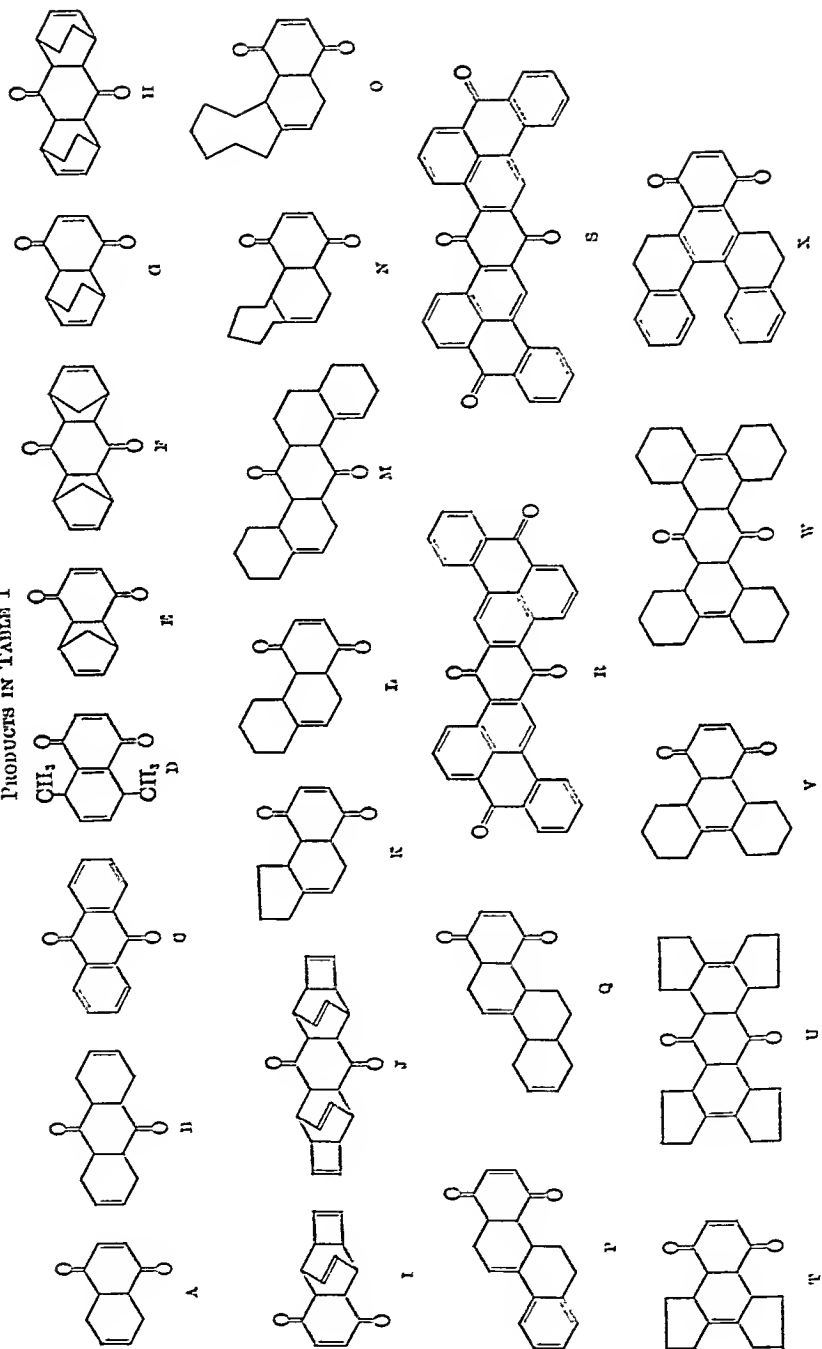


Since the structures of typical adducts have been adequately demonstrated, the products from analogous pairs of reactants are assumed to have analogous structures and are so entered in the tables, even though the structure of the particular compound was not proved. For reactions where the structure of the product has not been established but where a given structure is probable, the symbol is preceded by "probably." Where isomeric adducts are possible, the positions of the substituents will be identified by means of footnotes if these positions have been established.

The letter "t." in the column under "Temperature, °C" means that the reaction was carried out in a sealed tube.

In the column under "Yield," a dash (—) means that the yield was not recorded but does not necessarily mean that it was low. A "nearly quantitative" yield is entered as 100%. The yields usually refer to purified compounds, but there are some exceptions.

PRODUCTS IN TABLE I



PRODUCTS IN TABLE I—Continued

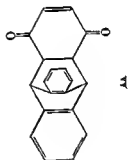
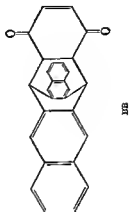
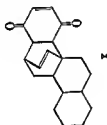
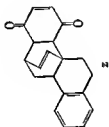


TABLE I
DIENE ADDITIONS TO *p*-BENZOQUINONE

| 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature, °C. | Hours | Product * | Yield % | Reference † |
|----------------------------|---|---------------------------------|------------------|-------|-----------|------------|-------------|
| Butadiene | Benzene | 1.1 | 35 | 3 | A | 100 | 2 |
| Butadiene | Water | 1 | 50 | 12 | A | 80 | 1 |
| Butadiene | — | 1.8 | 65 | — | A | — | 89, 38 |
| Butadiene | Benzene | >2 | 100 | 24 | B | — | 8 |
| Butadiene | None | 3 | 100t. | 3 | C † | — | 90 |
| Pentadiene | C ₆ H ₅ NO ₂ | 2 | 130t. | 7 | A | 16 | 91 |
| 2-Methylbutadiene | — | 1 | 50t. | — | A | — | 89, 38 |
| 2-Methylbutadiene | Ethanol | 3 | 100 | 12 | B § | — | 16 |
| 2,4-Hexadiene | Ethanol | 1 | 75t. | 6 | A | — | 91 |
| 2,4-Hexadiene | Pyridine and C ₆ H ₅ NO ₂ | 2 | 125t. | 12 | D | 16 | 91 |
| 2,4-Hexadiene | C ₆ H ₅ NO ₂ | 1 | 140t. | 6 | A | 35 | 91 |
| 2,4-Hexadiene | (<i>n</i> -C ₄ H ₉) ₂ O | 1 | 125-140t. | 24 | None | 0 | 91 |
| 2-Methylpentadiene | — | — | — | — | B | — | 92 |
| 2,3-Dimethylbutadiene | Water | 1 | 40 | 12 | A | 100 | 1 |
| 2,3-Dimethylbutadiene | — | 1 | 30t. | — | A | — | 89, 38 |
| 2,3-Dimethylbutadiene | — | 2.3 | Reflux | 1 | B | — | 93 |
| 2,3-Dimethylbutadiene | Ethanol | 2 | 97t. | 5 | B | 60 | 10 |
| 2,3-Dimethylbutadiene | C ₆ H ₅ NO ₂ | 2.3 | 150t. | — | C | — | 11 |
| 3,4-Dimethyl-2,4-hexadiene | None | — | 145 ¶ | 8 | B ** | 49 | 20 |
| 2-Chlorobutadiene | Water | 1 | 40 | 12 | A | 95 | 1 |

| | | | | | | |
|---|---|-----|-------------------|------|--|----|
| 1-Phenylbutadiene | Xylene | 2 | Reflux | 6 | A and B †† | 12 |
| 1-Phenylbutadiene | C ₆ H ₅ NO ₂ | 2 | 200 | 3 | C †† | 13 |
| 4-Phenylpentadiene | None | — | 105 | 2 | C ₂₅ H ₅₀ O ₂ | 94 |
| 4-(2',4'-Dimethylphenyl)- pentadiene | Benzene | — | 110 | 3 | C ₂₀ H ₃₄ O ₂ | 94 |
| 1,4-Diphenylbutadiene | None | 1 | — | 5 †† | C | 12 |
| 1,4-Diphenylbutadiene | C ₆ H ₅ NO ₂ | 2 | Reflux | — | C | 13 |
| 2,3-Diphenylbutadiene | Benzene | 1.4 | 100 | 18 | A | 95 |
| 1-Acetoxybutadiene | — | — | — | — | — | 96 |
| Cyclopentadiene | Ethanol | 1 | 5 | >1 | E | 14 |
| Cyclopentadiene | CCl ₄ | 1 | 40 | 8 | E | 15 |
| Cyclopentadiene | Benzene | 1 | 40 | 3 | E | 15 |
| Cyclopentadiene | Ethanol | 1 | 40 | 3 | E | 15 |
| Cyclopentadiene | n-Hexane | 1 | 40 | 6 | E | 15 |
| Cyclopentadiene | CS ₂ | 1 | 40 | 20 | E | 15 |
| Cyclopentadiene | C ₆ H ₅ OH or C ₆ H ₅ I | 2 | <Room temperature | — | E | 14 |
| Cyclohexadiene | None | 3.1 | Reflux | 0.23 | F | 97 |
| Cyclohexadiene | Benzene | 3.4 | Room temperature | 48 | G | 10 |
| Cyclohexadiene | None | 5 | Reflux | 24 | H | 8 |
| α-Terpinene (70%) | Ethanol | 0.4 | Reflux | 2 | G | 98 |
| α-Terpinene (94%) | Acetone | 1 | Reflux | 2 | Quinhydrone m.p. 170° | 98 |

* See pp. 164-165 for explanation of symbols in this column.

† References 80-123 are listed on p. 192.

‡ From the adduct by aeration in alkaline solution.

§ Both isomers.

|| One isomer; structure unknown.

¶ Previous reaction at 30-50°.

** Mixture of isomers.

†† Considered to be the 1,5-diphenyl isomer because of the high melting point of the anthraquinone to which it was dehydrogenated.

‡‡ The 1,5-diphenyl isomer.

§§ At slightly reduced pressure. The reaction was violent; the temperature was not measured.

TABLE I—Continued
DIENE ADDITIONS TO *p*-BENZOQUINONE

| 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature, °C | Hours | Product * | Yield % | Reference † |
|--|---|---------------------------------|------------------|-------|---|------------|-------------|
| α -Phellandrene | Ethanol | 1 | Reflux | 1.5 | G | — | 16 |
| Cyclooctatetraene | Xylene | — | 140 | — | I and J | — | 21 |
| 1-Vinylcyclopentene | — | — | — | — | K | — | 99 |
| 1-Vinylcyclohexene | Methanol | 1.5 | Reflux | 2 ‡ | L | — | 17 |
| 1-Vinylcyclohexene | Tetralin | 2.2 | Reflux | 0.2 | M | 10 | 17 |
| 1-Vinylcyclohexene | — | — | — | — | L | — | 99 |
| 1-Vinylcycloheptene | — | — | — | — | N | — | 99 |
| 1-Vinylcyclooctene | — | — | — | — | O | — | 99 |
| 4-Vinyl-1,2-dihydronaphthalene | Cyclohexane | — | 100 | — | P | — | 23 |
| 7-Methoxy-4-ethynyl-1,2-dihydronaphthalene | Cyclohexane | — | Room temperature | >48 | None | 0 | 23 |
| 7-Methoxy-1-vinyl-1,2-dihydronaphthalene | Cyclohexane | 1 | Room temperature | 36 | P | — | 23 |
| 4a-Methyl-1-vinyl-1,2,4a-5,8,8a-hexahydronaphthalene | Benzene | — | 50 | 24 | Q | — | 24 |
| 10-Methylene-9-anthrone | C ₆ H ₅ NO ₂ | 0.52 | Reflux | — | R or S | — | 40 |
| 10-Methylene-9-anthrone | Acetic acid | — | Reflux | — § | — | — | 55 |
| Styrene | None ¶ | 4 | — | 0.75 | Quinol and C ₂₂ H ₁₂ O ₂ ** | — | 100 |
| β -(1-Cyclohexenyl)naphthalene | — | — | — | — | C ₂₂ H ₁₀ ** | — | 101 |
| 1,1'-Bicyclopentenyl | Methanol | 1 | Reflux | 1 | T | — | 3 |

| | | | | | | | |
|---|---|-----|------------------|------|-------------------------------------|--------|---------|
| 1,1'-Bicyclopenteny] | Butanol | — | Reflux | 5 | U | 54 | 20 |
| 1,1'-Bicyclohexenyl | Ethanol | 1 | Reflux | 5 | V | — | 3 |
| 1,1'-Bicyclohexenyl | — | — | To reflux | — | W | — | 3 |
| 1,1'-Bicyclohexenyl | Butanol | — | Reflux | 8 | W | 58.5 | 20 |
| 1,1'-Bicyclohexenyl | None | 2 | 140 | 5 | W | 41 | 19 |
| 1,1'-Bicyclohexenyl | None | 5 | 100 | 5 | V †† | 86 | 18 |
| 1,1'-Bicyclohexenyl | — | — | 200 | 3 | — | 0 | 102 |
| Biphenyl | None | 0 1 | 150 | 3 | X †† | 80 | 18 |
| 3,4,3',4'-Tetrahydro-1,1'-bi-naphthyl | — | — | Room temperature | 48 | Y | — | 103 |
| 1-Pimaric acid | Benzene | — | Reflux | 0.2 | Z | — | 104 |
| Thiobane | Benzene | — | Reflux | 0.75 | AA | — | 25 |
| Anthracene | Xylene | 1 | Reflux | — | BB | 93 | 25, 105 |
| 2,3,6,7-Dibenzanthracene-9,10-diy] | None | 1 | — | — | — | — | — |
| α -Methylfuran | — | — | — | — | None | 0 | 106 |
| 2-Methylene-2,5-dihydrofuran | Benzene | — | Room temperature | 12 | CuH ₁₄ O ₂ †† | 2.1 g. | 106 |
| 2-Methylene-2,5-dihydrofuran | None | — | Room temperature | 48 | CuH ₁₄ O ₂ †† | 06 | 100 |
| Phenylcyclo [3,4-(2'-xenyleno)-2,5-diphenylcyclopentadienone] | C ₆ H ₅ NO ₂ | 2 | 100 | 2 | 1:2 Adduct | 50 | 56 |
| 1,3-Diphenylisobenzofuran | — | — | — | — | — | — | — |
| 1,3-Diphenylisobenzofuran | Ether | — | —10 | — | 1:1 Adduct | — | 107 |
| Isosafrole | Ethanol | — | Reflux | 2 | 1:2 Adduct | — | 108 |
| | — | — | — | — | — | 0 | 109 |

* See pp 104-105 for explanation of symbols in this column.

† References 89-133 are listed on p. 192.

‡ Stood overnight previously at room temperature.

§ Heating continued one-half hour after precipitation of red material ceased.

¶ Two products of undetermined structures.

‡ One-half gram of trichloroacetic acid added.

** Structure unknown.

†† Two isomers; structures unknown.

‡‡ A stable red crystalline compound apparently formed by the addition of 2 moles of quinone to 1 mole of 2-methylene-2,3-dihydrofuran.

§§ No addition when diene in excess or when dissolved in boiling benzene or xylene.

TABLE II
DIENE ADDITIONS TO METHYL-*p*-BENZOQUINONES

| <i>p</i> -Benzoquinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temper- ature °C | Hours | Product * | Yield % | Refer- ence † |
|------------------------|-------------------------|---|------------------------------------|------------------------|-------|-----------|------------|------------------|
| Methyl- | Butadiene | Benzene | 4 | 110 | 5 | A | 2.4 g. ‡ | 27 |
| Methyl- | Butadiene | Benzene | 1.9 | 70 | 6 | A | 84 | 26 |
| Methyl- | Pentadiene | Dioxane | 1.3 | 70 | 40 | A § | 44 | 28 |
| Methyl- | 2,3-Dimethylbutadiene | Benzene | 2.5 | Reflux | 4 | A | — | 29 |
| Methyl- | 2,3-Dimethylbutadiene | None | 2.5 | 110 | 1 | A | — | 29 |
| Methyl- | 2,3-Dimethylbutadiene | None | 2.5 | 170 | — | CC | 93 | 29 |
| Methyl- | 2,3-Dimethylbutadiene | None | 1.2 | Reflux | 36 | DD | 17 | 53 |
| Methyl- | 10-Methylene-9-anthrone | Acetic acid | 5 | Reflux | — | — | — | 55 |
| 2,3-Dimethyl- | 2,3-Dimethoxybutadiene | None | 0.5 | 140 | 36 | DD | 82 | 110 |
| 2,3-Dimethyl- | 2,3-Dimethylbutadiene | Ethanol | 3 | Reflux | 8 | A | 80 | 26 |
| 2,5-Dimethyl- | Butadiene | Ethanol | 5 | 100 | 62 | A ¶ | 75 | 30 |
| 2,5-Dimethyl- | Butadiene | Benzene | — | 110 | 5 | None | 0 | 27 |
| 2,5-Dimethyl- | Butadiene | Benzene | 4 | 170 | 10 | B | 10 | 4 |
| 2,5-Dimethyl- | 2,3-Dimethylbutadiene | Ethanol | 4 | 100 | 27 | A ¶ | 66 | 30 |
| 2,5-Dimethyl- | 2,3-Dimethylbutadiene | Ethanol | 4 | 100 | 72 | A ¶ | 77 | 30 |
| 2,5-Dimethyl- | 2,3-Dimethylbutadiene | Benzene | 4 | 100 | 72 | A ¶ | 85 | 30 |
| 2,5-Dimethyl- | 1,3,5-Hexatriene | Ethanol | 1.5 | 163 | 26 | A ¶ | 57 | 35 |
| 2,5-Dimethyl- | Cyclohexadiene | Ethanol | 1.5 | 80-104 | 72 | Q | 1 | 7 |
| 2,5-Dimethyl- | 2,3-Dimethylbutadiene | C ₆ H ₆ + C ₂ H ₅ OH | 4 | 100 | 87 | A | 82 | 30 |

* See p. 170 for explanation of symbols used in this column.

† References 89-133 are listed on p. 102.

‡ Erroneous; the theoretical yield is 1.75 g.

§ Both the 2,5- and 2,8-dimethyl isomers.

|| The 2,6,7-trimethyl isomer.

¶ A liquid.

TABLE II—Continued
DIENE ADDITIONS TO METHYL-*p*-BENZOQUINONES

| <i>p</i> -Benzoquinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C | Hours | Product * | Yield % | Reference † |
|--|--|---|---|--|---|---|--|---|
| 2-Isopropyl-5-methyl-2-acetoxy-5-methyl-2-acetoxy-5-methyl-2-acetoxy-5-methyl-2-acetoxy-5-methyl-2-acetoxy-5-methyl-2-acetoxy-5-methyl-2-carbamethoxy-5-methyl-2-carbamethoxy-5-methyl-2-methoxy-5-methyl-2-hydroxy-3,5-dimethyl-2-hydroxy-4,5-dimethyl- | Pentadiene 2,3-Dimethylbutadiene Butadiene 2,3-Dimethylbutadiene 1,3,5-Hexatriene 1,3,5-Hexatriene 1,4,5-Hexatriene Cyclohexadiene Butadiene Butadiene Butadiene 7-Methoxy-1-vinyl-1,2-dihydronaphthalene 1,3,5-Hexatriene 1,3,5-Hexatriene 1,3,5-Hexatriene | Ethanol Ethanol Ethanol Ethanol Ethanol Ethanol Ethanol Benzene Benzene Ethanol Dioxane Dioxane Ethanol Benzene Benzene | — 3 2 1.5 3 3 3 2.3 4 2 4.2 15 — 2 1.2 1.5 | 100 100 75 95 74 73 97 65 100 100 100 110 120 100 150 204 | 112 >24 68 144 396 396 164 654 16 66 65 204 154 434 65 3 | A † A † A ‡ A ‡ A ‡ A ‡ A ‡ G ‡ A ‡ A ‡ A ‡ A ‡ or F ‡ None Duroquinol Duroquinol | 75.5 — 25 42 45 21 6 55 77 78 75 100 — 0 — 42 | 30 30, 43 32 33 33 33 33 33 33 34 34 7 5 5 35 35 35 |

* See p. 170 for explanation of symbols used in this column.

† References 89-433 are listed on p. 162.

‡ A liquid.

§ Isolated as the free enol from the angular methyl product.

|| The 5-acetoxy-2,7,8-trimethyl isomer.

¶ The angular acetate.

** Possibly the 2-hydroxy-6-methyl-6-vinyl isomer.

†† An enol acetate.

‡‡ Three compounds obtained. Yields of crystalline substances: angular acetate, 55%; stereoisomeric angular acetate, 6%; enol (2-hydroxy-5-methyl derivative), 1%.

§§ The angular carboxylate.

||| The angular methyl isomer.

¶¶ The 3-hydroxy-2,10-dimethyl isomer.

*** The 3-hydroxy-2,14-dimethyl isomer.

PRODUCTS IN TABLE III

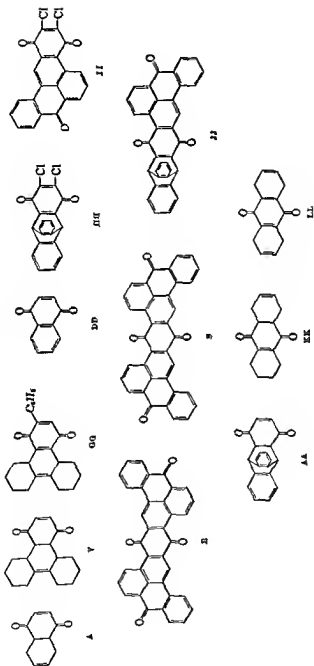


TABLE III
DIENE ADDITIONS TO SUBSTITUTED *p*-BENZOQUINONES OTHER THAN METHYL-*p*-BENZOQUINONES

| <i>p</i> -Benzoquinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature, °C | Hours | Product * | Yield % | Reference † |
|------------------------|-------------------------|--|---------------------------|------------------|-------|---|---------|-------------|
| Phenyl- | 2,3-Dimethylbutadiene | None | 5.5 | 100 | 1 | A ‡ | 82 | 29 |
| Phenyl- | Cyclopentadiene | Benzene | 1 | Reflux | 2 | A ‡ | 18 | 29 |
| Phenyl- | 1,1'-Bicyclohexenyl | None | 0.9 | 120-150 | 4 | V ‡ | — | 19 |
| Phenyl- | 1,1'-Bicyclohexenyl | C ₆ H ₆ .NO ₂ | 0.9 | Reflux | 4 | GG | — | 19 |
| 2,3-Diallyl- | 2,3-Dimethylbutadiene | — | — | — | — | DD § | — | 111 |
| ω-Carboxypropyl- | Butadiene | Benzene | 30 | 70 | 8 | A ¶ | 56 | 37 |
| ω-Carboxyamyl- | Butadiene | Benzene | 10 | 70 | 6 | A ¶ | 75 | 37 |
| Chloro- | 2,3-Dimethylbutadiene | — | — | 60 | — | A ¶ | — | 38 |
| Chloro- | 2-Chlorobutadiene | Water | 1 | 40 | 12 | A ** | — | 1 |
| 2,3-Dichloro- | Butadiene | — | — | 100 | — | A †† | — | 38 |
| 2,3-Dichloro- | 2,3-Dimethylbutadiene | — | — | Room temperature | — | A †† | — | 38 |
| Tetrachloro- | Cyclopentadiene | Benzene | 2 | Room temperature | 336 | C ₁₁ H ₆ O ₂ Cl ₄ | — | 14 |
| Tetrachloro- | Cyclopentadiene | Benzene §§ | — | 29 | 24 | C ₁₁ H ₆ O ₂ Cl ₄ | 72 | 30 |
| Tetrachloro- | Anthracene | Xyleno or acetic acid | 1 | Reflux | — | III | — | 23 |
| Tetrachloro- | Anthracene | None | 1 | 250 | 0.5 | III | — | 25 |
| Tetrachloro- | Pentacene-9,10-diyl | Xyleno | 1 | Reflux | — | — §§ | — | 25, 105 |
| Tetrachloro- | 10-Methylene-9-anthrono | Xyleno | 0.9 | Reflux | — | II | — | 40 |

| | 10-Methylene-9-anthrone | $C_6H_5NO_2$ | 0.5 | Reflux | — | R or S | — | 40 |
|---------------------------------------|-------------------------|--------------|-----|--------|--------------------------|-------------------|-----|--------|
| Tetrachloro- | 10-Methylene-9-anthrone | Acetic acid | 5 | Reflux | — | Contains chlorine | — | 55 |
| Trichloro- | 10-Methylene-9-anthrone | — | — | — | — | — | — | — |
| AA * | 10-Methylene-9-anthrone | Xylene | 0.3 | Reflux | 1 | JJ | 100 | 40 |
| AA * | Anthracene | Xylene | 0.8 | Reflux | 1 | 1:1 Adduct | 90 | 25 |
| 5,6,7,8-Tetrahydro-1,4-naphthoquinone | Butadiene | None | 2 | 80° | — | KK | — | 38, 41 |
| 5,8-Dihydro-1,4-naphthoquinone | Butadiene | None | 2 | 80° | — | LL | — | 38, 41 |
| 2,5-Diphenyl- | Butadiene | Ethanol | — | 90 | 96 | A | 77 | 36 |
| 2,5-Diphenyl- | 2,3-Dimethylbutadiene | Ethanol | — | Reflux | 144 | A | 79 | 36 |
| 2,5-Diphenyl- | 1-Phenylbutadiene | Ethanol | — | Reflux | 24 | A ¶¶ | 89 | 36 |
| 2,5-Diphenyl- | 1-Phenyl-1,3-pentadiene | — | — | — | — | Mixture | — | 30 |
| 1-Keto-2,3-diphenylindene-4,7-quinone | Cyclopentadiene | Benzene | 2 | Reflux | Time to distil to 10 ml. | The 3a, 7a-adduct | 73 | 112 |

* See p. 172 for explanation of the symbols in this column.

† References 83-133 are based on p. 192.

‡ The 2-phenyl isomer.

§ The adduct was monomerized to a hydroquinone which was oxidized by chromic acid to 2,3-diallyl-6,7-dimethyl-1,4-naphthoquinone.

|| Probably the 2-carboxyethyl isomer.

¶ Probably the 2-chloro-6,7-dimethyl isomer.

** The 2,7-dichloro isomer.

†† Probably the 2,3-dichloro isomer.

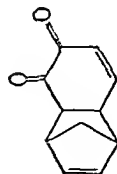
‡‡ The 2,3-dichloro-6,7-dimethyl isomer.

§§ Traces of trichloroacetic acid added.

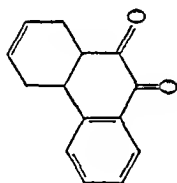
||| Normal adduct plus by-product.

¶¶ Formulated without evidence as the 2,5,9-triphenyl derivative.

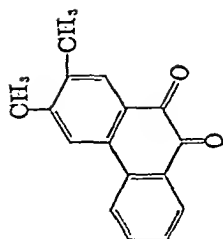
PRODUCTS IN TABLE IV



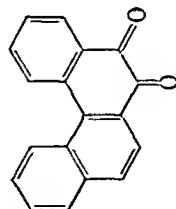
MM



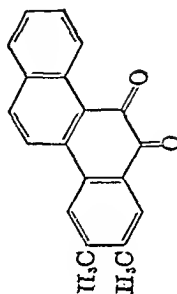
NN



OO



PP



QQ

TABLE IV
DIENE ADDITIONS TO *o*-QUINONES

| Quinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C | Hours | Product * | Yield % | Reference † |
|--------------------------------|-------------------------|-------------------|---------------------------|----------------|-------|-----------|--------------|-------------|
| <i>o</i> -Benzo- | Cyclopentadiene | — | — | — | — | — | — | 42 |
| Tetramethyl- <i>o</i> -benzo- | Cyclopentadiene | 95% ethanol | 2.5 | Reflux | 1 | MM | 63 | 42 |
| 1,2-Naphtho- | 1-Picene acid (crude) | — | — | — | — | — | — | 114 |
| 1,2-Naphtho- | 10-Methylene-9-anthrone | Acetic acid | — | Reflux | — | — ‡ | — | 55 |
| 1,2-Naphtho- | ? | — | — | — | — | — § | — | 113 |
| 3,7-Dimethyl-1,2-naphtho- | 2,3-Dimethylbutadiene | Ethanol | 5 | 100 | >24 | NN | 93 | 44 |
| 3,7-Dimethyl-1,2-naphtho- | 2,3-Dimethylbutadiene | Ethanol | — | Heated | 63 | NN | 83 | 30 |
| 4-Benzyl-1,2-naphtho- | 2,3-Dimethylbutadiene | Ethanol | — | 100 | 72 | NN | 0.5 g. crude | 115 |
| 4-Diacetoxymethyl-1,2-naphtho- | 2,3-Dimethylbutadiene | Ethanol | — | 100 | 120 | NN | — | 115 |
| 3-Bromo-1,2-naphtho- | 2,3-Dimethylbutadiene | CHCl ₃ | 3.5 | 100 | 2 | OO | 76 | 45 |

* See p. 176 for explanation of symbols in this column.

† References 80-123 are listed on p. 192.

‡ Constitution unknown.

§ Addition occurs.

|| By dehydrogenation of the ally adduct with chromic acid in acetic acid.

TABLE IV—Continued

| Quinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C | Hours | Product * | Yield % | Reference † |
|---|-----------------------|-------------------|---------------------------|----------------|-------|------------|---------|-------------|
| 6-Bromo-1,2-naphtho- | 2,3-Dimethylbutadiene | — | — | — | — | NN | 45 | 45 |
| 3-Chloro-1,2-naphtho- | 2,3-Dimethylbutadiene | CHCl ₃ | 3.5 | 100. | 1 | NN ‡ | 70 | 45 |
| 4-Chloro-1,2-naphtho- | 2,3-Dimethylbutadiene | CHCl ₃ | 3.5 | 100 | 72 | OO § | 15 | 45 |
| 3,4-Dichloro-1,2-naphtho- | 2,3-Dimethylbutadiene | CHCl ₃ | 5 | 100 | 60 | NN | 24 | 45 |
| 2,3-Dimethyl-1,4-dihydro-9,10-phenanthra- | 2,3-Dimethylbutadiene | CHCl ₃ | 4.5 | 100 | 2 | 1:1 Adduct | 36 | 46 |
| 1,2-Phenanthra- | 2,3-Dimethylbutadiene | CHCl ₃ | 34 | — | 48 | PP | 29 | 46 |
| 3-Bromo-1,2-phenanthra- | 2,3-Dimethylbutadiene | CHCl ₃ | 15 | — | 3 | PP | 79 | 46 |
| 2-Bromo-3,4-phenanthra- | 2,3-Dimethylbutadiene | CHCl ₃ | 10 | 100 | 2 | QQ ¶ | 99 | 46 |
| 3-Bromo-1,2-phenanthra- | Butadiene | CHCl ₃ | 13 | — | 5 | PP | 65 | 46 |

* See p. 170 for explanation of the symbols in this column.

+ References 80-133 are listed on p. 102.

* In unstable; when warmed with ethanol/s sodium acetate, gives a quantitative yield of 2,3-dimethyl-9,10-phenanthraquinone.

4 is mistaken, when written with ordinary pointing and

|| With exposure to sunlight, ||

By dehydration of the crude adduct with chromic acid in aqueous acetic acid.

PRODUCTS IN TABLE V

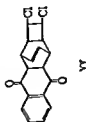
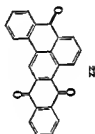
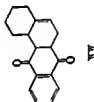
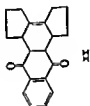
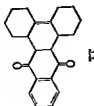
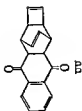


TABLE V
DIENE ADDITIONS TO 1,4-NAPHTHOQUINONE

| 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C. | Hours | Product * | Yield % | Refer- ence † |
|-------------------------------|---------------------------|---------------------------------|--------------------|-------|-------------|------------|------------------|
| Butadiene | Ethanol | 1:2 | 100 | 3 | RR | — | 16, 48 |
| Isotactadiene | Benzene | 1:2 | 70 | 2.5 | RR | — | 47 |
| 2-Methylbutadiene | Ethanol | 1:5 | 100 | 4 | RR | — | 16 |
| 2-Methylbutadiene | Ethanol | 2:3 | 80 | 8 | C ‡ | 100 | 57 |
| 2,3-Dimethylbutadiene | Ethanol | — | 70 | — | RR | — | 57 |
| 2,3-Dimethylbutadiene | Ethanol | — | Reflux | 5 | RR | 96 | 58 |
| 2,3-Dimethylbutadiene | None | 2:3 | Reflux | 1 | RR | — | 58 |
| 2,3-Dimethylbutadiene | CdH_5NO_2 | — | — | — | C | — | 11 |
| 2-Methylpentadiene | Ethanol | 4 | Reflux | 2 | RR | — | 16, 47 |
| 2,4-Dimethylpentadiene | None | 5 | Reflux | 6 | RR | — | 16 |
| 2,4-Dimethylpentadiene | None | — | Reflux | 8 | RR | 62 | 116 |
| 2,4-Dimethylpentadiene | Dioxane | — | 110 | 24 | RR | 13 | 116 |
| 2,5-Dimethyl-2,4-hexadiene | — | — | — | — | — | 0 | 116 |
| 3,6-Dimethyl-3,5-octadiene | — | — | — | — | — | — | 116 |
| Myrcene | Dioxane | — | Reflux | 12 | RR § | 64 | 116 |
| 1,3,5-Hexatriene | Ethanol | 1:5 | 50 | 6 | RR § | 100 | 118 |
| 2,5-Dimethyl-1,3,5-hexatriene | — | — | — | — | No reaction | — | 117 |
| 2,6-Dimethyl-2,4,6-octatriene | — | — | — | — | RR ¶ | — | 119 |
| 1-Chlorobutadiene | — | — | — | — | No reaction | — | 49 |

| | Benzene | 2.4 | Reflux + room temperature Room temperature + reflux | 3 + 16 | RR † | |
|-------------------------------------|----------------------|-----|--|--------|-------------|-----|
| 2-Chlorobutadiene | Benzene | 2 | 100 | 48 + 1 | RR | 50 |
| 2-Bromobutadiene | Benzene | — | 100 | — | — | 61 |
| 3-Chloropentadiene | — | — | 100 | 2 | C ** | 52 |
| 3-Chloro-1,3-hexadiene | — | — | 100 | 2 | C ** | 52 |
| 3-Chloro-1,3-octadiene | — | — | 100 | 2 | C ** | 52 |
| 3-Chloro-1,3-hendecadiene | — | — | 100 | 2 | C ** | 52 |
| 2,3-Dichlorobutadiene | — | — | — | — | No reaction | 49 |
| 2-Chloro-3-methylbutadiene | None | — | 100 | 0.5 | RR | 54 |
| 2-Chloro-3-methylpentadiene | None | — | 100 | 1 | RR | 54 |
| 1,3,4,6-Tetrachloro-2,4-hexadiene | — | — | 100 | — | No reaction | 49 |
| 2-Acetoxybutadiene | None | — | 100 | 1.5 | C †† | 120 |
| 1-Acetoxybutadiene | — | — | — | — | — | 6 |
| 2-Ethoxybutadiene | Benzene | — | Reflux | 6 | C ** | 121 |
| 1-Hydroxybutadiene (crotonaldehyde) | Benzene + piperidine | — | — | — | C | 122 |
| 2-Chloro-1-hydroxybutadiene | Benzene + piperidine | — | — | — | C | 122 |
| 1-Hydroxy-2-methylbutadiene | Benzene + piperidine | — | — | — | C | 122 |
| 2,3-Dimethoxybutadiene | Benzene | 1 | Reflux | 8 | C †† | 53 |

* See p. 179 for explanation of symbols in this column.

† References 82-133 are listed on p. 192.

‡ By aeration of the crude adduct in boiling 5% potassium hydroxide.

§ A liquid.

|| Converted to 0,10-diketo-1,1-dimethyl-4-(α -methylpropenyl)-3,4-dihydroanthracene by aeration in potassium hydroxide solution.

¶ Not entirely pure.

** Added in alkaline solution without isolation.

†† The crude crystalline adduct was oxidized in alkaline solution.

‡‡ A solution of the adduct in ethanol was dehydrogenated with aqueous sodium hypochlorite.

TABLE V—Continued
DIENE ADDITIONS TO 1,4-NAPHTHOQUINONE

| 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C. | Hours | Product * | Yield % | Reference † |
|--|---|---------------------------|-----------------|-------|------------|---------|-------------|
| 2,3-Diethoxybutadiene | Benzene | — | Reflux | 6 | C ‡ | — | 53 |
| 1-Phenylbutadiene | Nono | — | — | — | C | — | 16 |
| 1-Phenylbutadiene | C ₆ H ₅ NO ₂ | 1.2 | 180 | 5 § | C | 47 | 13 |
| 1,4-Diphenylbutadiene | Nono | — | 160 | 10 | C | — | 12 |
| 1,4-Diphenylbutadiene | C ₆ H ₅ NO ₂ | 1.7 | Reflux | 2 | C | 70 | 13 |
| 2,3-Diphenylbutadiene | Xylene | 1 | Reflux | 2.5 | RR | 74 | 95 |
| Cyclopentadiene | Benzene | — | 5 | — | SS | — | 14 |
| Cyclohexadiene | Nono | 3.3 | Reflux | 2 | TT | — | 16 |
| Cyclohexadiene | Nono | 3.75 | Reflux | — | TT | — | 123 |
| Cyclohexadiene | Nono | 1.5 | 50 | 6h. | TT | 70 | 118 |
| Cyclohexadiene | Ethanol | — | Reflux | 2 | TT | — | 16 |
| α-Phellandrene | Ethanol | — | >100 | — | UU | — | 21 |
| Cyclooctatetraene | — | — | — | — | VV | — | 21 |
| 7,8-Dichlorobicyclo[0.4.2]octa-2,4-diene | — | — | — | — | 1:1 Adduct | — | 99 |
| 1-Vinylcyclopentene | — | — | — | — | 1:1 Adduct | — | 99 |
| 1-Vinylcyclohexene | — | — | — | — | 1:1 Adduct | — | 99 |
| 1-Vinylcycloheptene | — | — | — | — | 1:1 Adduct | — | 99 |
| 1-Vinylcyclooctene | — | — | — | — | 1:1 Adduct | — | 51 |
| α-Chlorovinylcyclohexene | Nono | — | 100 | 0.33 | WW | — | 109 |
| Isosafrole | — | — | — | — | — | 0 | — |

| | None | 2 | 110 | 0.75 | 1:1 Adduct | |
|---|---|-----|------------------|------|-------------------------|---------|
| 4a-Methyl-4-vinyl-1,2,4a,5,8,8a-hexahydronaphthalene | None | — | Reflux | 1 | XX | 67 |
| 1,1'-Bicyclopentenyl | Ethanol | — | To reflux | — | YY | 3 |
| 1,1'-Bicyclohexenyl | None | — | 150t. | 3 | — II | 3 |
| 1,1'-Bicyclohexenyl | — | 5 | 100 | 2 | YY | 19 |
| 3,4,3',4'-Tetrahydro-1,1'-binaphthyl | None | 0.5 | 130 | 3 | 1:1 Adduct | 18 |
| 10-Methylene-9-anthrone | Ethanol | — | Reflux | — | ZZ | 18 |
| 10-Methylene-9-anthrone | C ₆ H ₅ NO ₂ | 1 | Reflux | — | ZZ | 55 |
| 1-Chloro-10-methylene-9-anthrone | Acetic acid | — | Reflux | — | Chloro derivative of ZZ | 40 |
| 2,5-Diphenyl-3,4-(2,2'-xenylene)cyclopentadienone (phenylcyclo) | C ₆ H ₅ NO ₂ | — | 100 | 4 | 1:1 Adduct † | 55 |
| Tetraphenylcyclopentadienone (cyclo) ** | Ethanol | — | 180t. | — | None | 50, 130 |
| Tetraphenylcyclopentadienone ** | Toluene | — | 220t. | — | None | 56 |
| Tetraphenylcyclopentadienone ** | C ₆ H ₅ NO ₂ | — | 160-200 | — | None | 56 |
| 1,3-Diphenylisobenzofuran | Xylene | 1 | Reflux | 2 | 1:1 Adduct | 124 |
| 1,3-Diphenylisobenzofuran | None | — | Room temperature | — | 1:1 Adduct | 125 |
| 1-Penten-3-yne | None | >1 | 100t. | 2 | None | 126 |

* See p. 179 for explanation of symbols in this column.

† References 82-133 are listed on p. 192.

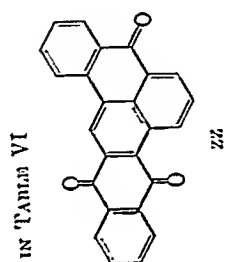
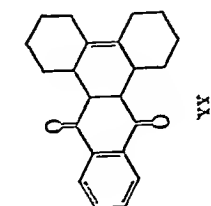
‡ The crude adduct was aerated in sodium hydride solution.

§ Minutes.

|| 1,4-Naphthohydroquinone; a diketododecahydrodibenzanthracene and a diketododecahydrodibenzanthracene (probably 1,2,3,4-dibutano-9,10-anthraquinone) were isolated.

¶ Converted to 1,4-diphenyl-2,3-(2,2'-xenylene)-9,10-anthraquinone by air and ethanol; alkali, nitrobenzene, or chromic acid.

** Anacyclone, 3,4-(1,8 naphthylene)-2,5-diphenylcyclopentadienone, gave similar results.



PRODUCTS IN TABLE VI

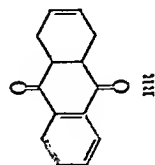
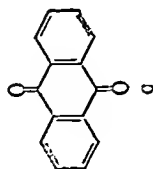


TABLE VI
DIENE ADDITIONS TO SUBSTITUTED 1,4-NAPHTHOQUINONES

| 1,4-Naphthoquinone | 1,3-Diene | Solvent | Ratio of Diene to Quinone | Temperature °C. | Hours | Product * | Yield % | Reference † |
|---|--|---|---------------------------|---------------------------------|------------------------------|---|--------------------------|----------------------------|
| 2-Methyl-2,3-dimethyl-2,6-dimethyl-2,6-dimethyl-2-chloro- | — 2,3-Dimethylbutadiene 2,3-Dimethylbutadiene Pentadiene Butadiene | Ethanol Ethanol Ethanol Ethanol — | 6 5 5 — — | 100 100 100 100 125 | >24 100 >24 96 — | RR ‡ RR ‡ RR RR ‡ 9,10-Diketo-1,4-dihydroanthracene | — — 100 45 — | 43 43 43 30 57 |
| 2-Chloro-2-chloro-2-chloro- | 2-Methylbutadiene 2,3-Dimethylbutadiene 10-Methylene-9-anthrone | — Ethanol Sodium acetate-acetic acid (1:10) | — — — | 120t. 105t. Reflux | 5 5 — | C C ZZ | — — — | 57 57 55 |
| 2,3-Dichloro-2,3-Dichloro- | 2,3-Dimethylbutadiene 10-Methylene-9-anthrone | — Sodium acetate-acetic acid (1:10) | — — | — Reflux | — — | RR § ZZ | — — | 57 55 |

* See p. 184 for explanation of symbols in this column.

† References 89-133 are listed on p. 192.

‡ A liquid.

§ Converted to 2,3-dimethyl-9,10-anthraquinone by heating with ethanolic potassium hydroxide.

TABLE VI—Continued
DIENE ADDITIONS TO SUBSTITUTED 1,4-NAPHTHOQUINONES

| | 1,3-Dieno | Solvent | Ratio of Dieno to Quinone | Tem- pera- ture °C. | Hours | Product * | Yield % | Refer- ence † |
|--|---|---|------------------------------------|---------------------------------|--------------------------------|---|----------------------------|----------------------------|
| 1,4-Naphthoquinone | | | | | | | | |
| 2,3-Dichloro-5-Amino-2,3-Dichloro-5-nitro- | 10-Methylene-9-anthrono 2,3-Dimethylbutadiene Butadiene | C ₆ H ₅ NO ₂ Ethanol — | — — — | Reflux Reflux 130 | — 2 2 | ZZ RR 1-Amino- 9,10-anthra- quinone ‡ RR | — — — | 40 57 57 |
| 2,3-Dichloro-5-nitro-5,6,11,12-Naphthacenediaquinone | 2,3-Dimethylbutadiene Butadiene | — — | — — | — — | — — | 1:1 Adduct RR | — 74.5 | 57 58 |
| 5,6,11,12-Naphthacenediaquinone | 2,3-Dimethylbutadiene | Acetic acid | — | 100 | 5 | 1:1 Adduct | 87 | 58 |
| 2-Hydroxy-2-Methoxy-5-Hydroxy-5-Hydroxy-5-Acetoxy- | 2,3-Dimethylbutadiene 2,3-Dimethylbutadiene Butadiene 2,3-Dimethylbutadiene 2,3-Dimethylbutadiene | Ethanol Ethanol Ethanol Ethanol Ethanol | — — 10 6 6 | 100 100 100 100 100 | 22 66 0.5 0.33 0.5 | C § C § RR RR RR | 70 80 94 95 94 | 30 30 45 45 45 |
| 5,8-Dihydroxy-5,8-Diacetoxy- | 2,3-Dimethylbutadiene 2,3-Dimethylbutadiene | Ethanol Ethanol | 17.5 40 | 100 100 | 6 3 | RR RR | 83 92 | 45 45 |
| { 2,5,8-Trihydroxy-5,6,8-Trihydroxy- | 2,3-Dimethylbutadiene | Ethanol | 15 | 100 | 60 | RR | 33 | 45 |

| | | | | | | | | |
|---|--------------------------------|---|-----|--------|-----|---------------|------|----------|
| 5,8,8-Triacetoxy- 2-Methyl-8-hydroxy- | 2,3-Dimethylbutadiene | Ethanol | 53 | 100 | 27 | RR | 70 | 45 |
| 5,8-Dihydroxy- | 2,3-Dimethylbutadiene | Ethanol | 6.4 | 100 | 19 | RR | 84 | 45 |
| 5,8-Dihydroxy- | Butadiene | Benzene | 1 | 100 | 6 | RR † | — | 57 |
| 5,8-Dihydroxy- | 2,3-Dimethylbutadiene | Benzene | 1 | 100 | 6 | RR † | — | 57 |
| 5,8-Dihydroxy- | 2,3-Dimethylbutadiene | — | — | 65 | — | RR | — | 127 |
| 5,8-Dihydroxy- | Pentadiene | C ₆ H ₅ NO ₂ | — | 130L | 20 | C | 43 | 128, 129 |
| 5,8-Dihydroxy- | 2,4-Hexadiene | C ₆ H ₅ NO ₂ | — | 170L | 2 | C | 74 | 128, 129 |
| 5,8-Dihydroxy- | 2,6-Dimethyl-1,3,5-heptatriene | Ethanol + CO ₂ | — | 50L | 8 | RR ** | 20.5 | 128, 129 |
| 5,8-Dihydroxy | 2,6-Dimethyl-1,3,5-heptatriene | Benzene | — | 50 | 12 | RR ** | 9 | 129 |
| 5,8-Dihydroxy- | Phencyclone | — | — | — | — | 1:1 Adduct | — | 130 |
| 5,8-Diacetoxy- | Pentadiene | Ethanol | — | 100 | 5 | RR | — | 131 |
| 5,8-Diacetoxy- | 2-Methylbutadiene | Ethanol | — | 100 | 5 | RR | — | 131 |
| 5,8-Diacetoxy- | 1,1'-Bicyclohexenyl | Toluene | 1 | Reflux | 2.5 | YY | — | 3 |
| 5,8-Dihydroxy-6-(1'-methoxy-4'-methyl-3'-pentenyl) [al-kannin methyl ether] | 2,3-Dimethylbutadiene | Ethanol | — | Reflux | 2 | 1:1 Adduct †† | — | 132 |

* See p. 154 for explanation of symbols in this column.

† References 89-133 are listed on p. 197.

‡ By treatment with potassium hydrosulfide, sodium hydrosulfite, and air.

§ From the adduct after aeration in ethanolic potassium hydrosulfide.

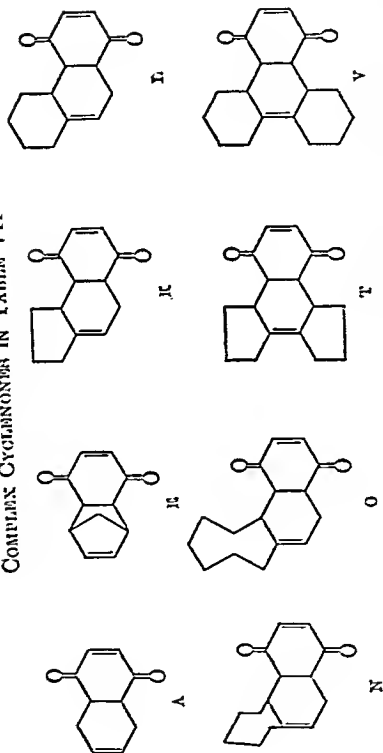
|| The isomer to be expected from 5,8,8-trihydroxy-1,4-naphthoquinone.

¶ Not purified.

** Probable structure.

†† Aeration in ethanolic potassium hydrosulfide gave the anthraquinone, C₁₄H₈O₄, resulting from dehydrogenation and elimination of methanol.

COMPLEX CYCLENONES IN TABLE VII *



* Many of the 1:1 adducts from *p*-benzoquinone and a variety of dienes can add a second nido of diene. Because of the complexity of their names, the original symbols by which they were identified in Table I are used for their designation in the column labeled "Cyclenones."

PRODUCTS IN TABLE VII

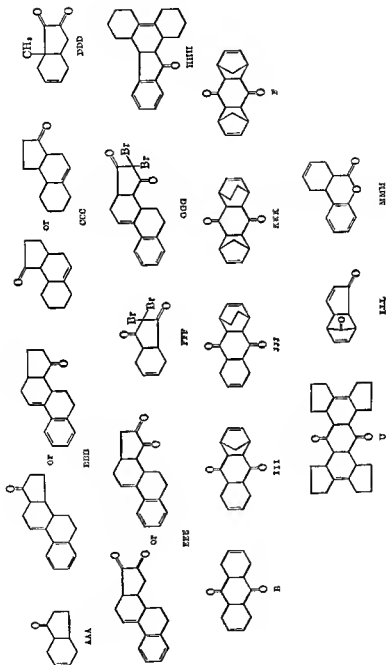


TABLE VII
DIENE ADDITIONS TO CYCLENONES OTHER THAN QUINONES^a

| Cyclonone | 1,3-Diene | Solvent | Ratio of Diene to Cyclonone | Temperature °C. | Hours | Product * | Yield % | Reference † |
|----------------------------------|--|-----------------|-----------------------------|-----------------|-------|-------------------------------------|------------|-------------|
| Cyclopenten-3-ono | Butadiene | Dioxane | 3 | 120-160 | 40 | AAA ‡ | — | 59 |
| Cyclopenten-4-ono | 6-Methoxy-1-vinyl-3,4-dihydronaphthalene | Dioxane | 1.1 | 120 | 40h. | HHB | — | 59 |
| 1-Methyleyclopenten-5-ono | 2,3-Dimethylbutadiene | CO ₂ | 0.9 | 200h. | 15 | AAA ‡ | — | 60 |
| 1-Methyleyclopenten-5-ono | Vinylcyclohexene | N ₂ | 0.2 | 170h. | 16 | CCC ‡ | 52 | 60 |
| 1-Methyleyclopenten-5-ono | Vinylcyclohexene | N ₂ | 0.3 | 205h. | 24 | CCC ‡ | 75 | 60 |
| 1-Methyleyclopenten-5-ono | 1-Vinyl-3,4-dihydronaphthalene | N ₂ | 0.18 | 160h. | 22 | BBB ‡ | — | 60 |
| 1-Methyleyclopenten-5-ono | 6a-Methyl-1-vinyl-1,2,4a,5,8a-hexahydronaphthalene | None | 10 | 200 | 48 | Dimethyl-steroidione | — | 61 |
| 1-Methyleyclopenten-4,5-diono | Butadiene | Dioxane | 18 | 130 | 40 | DDD | — | 62 |
| 1-Methyleyclopenten-4,5-diono | Butadiene | Dioxane | 1.8 | 130 | 40 | DDD | — | 62 |
| 1-Methyleyclopenten-4,5-diono | 6-Methoxy-1-vinyl-3,4-dihydronaphthalene | Dioxane | 2 | 115 | 50 | EEE | 30 (crude) | 5, 6 |
| 4,4-Dibromocyclopenten-3,5-diono | Butadiene | Dioxane | 5 | 115 | 24 | FFF | — | 59 |
| 4,4-Dibromocyclopenten-3,5-diono | 6-Methoxy-1-vinyl-3,4-dihydronaphthalene | Dioxane | 5 | 115 | 24 | GGG | 12 | 59 |
| Cyclohexen-3-ono | Butadiene | None | 2.3 | 190 | 72 | An octalone | 11 | 63 |
| Cyclohexen-3-ono | 2,3-Dimethylbutadiene | None | 1.5 | 200 | 72 | An octalone | 20 | 63 |
| Cyclohexen-3-ono | 1-Methyl-2-vinylcyclohexene | — | — | — | — | C ₁₅ H ₁₆ O § | — | 64 |
| Cyclohexen-3-ono | Cyclohexadiene | None | 2.5 | Reflux | 22 | None | 0 | 65 |
| 1-Methyleyclohexen-3-ono | Butadiene | — | — | — | — | None | 0 | 66 |

| | | | | | | | | | |
|--|--|---------|-----|--------|----|---------|-----------------------|---------|-----------|
| 1-Methylcyclohexen-3-one | 1,3,5-Hexatriene | — | — | — | — | — | None | 0 | 66 |
| 1-Methylcyclohexen-6-one | Butadiene | None | — | — | — | — | An octalone | — | 67 |
| 1-Methylcyclohexen-6-one | Butadiene | — | 0.4 | 200 | — | — | A 9-methyl-octalone-1 | 25 | 133 |
| 2,3-Dimethylindone | 1,1'-Dicyclohexenyl | Toluene | — | 200 | 8 | — | HHH | — | 19 |
| A ¹ | Butadiene | None | — | 100 | — | — | B | — | 38 |
| A | 2,3-Dimethylbutadiene | None | — | 100 | — | — | B | — | 38, 41 |
| A | Cyclopentadiene | — | — | — | — | — | III | — | 8 |
| I ¹ | Cyclohexadiene | None | 6 | Reflux | 24 | — | JJJ | — | 8 |
| L ¹ | Cyclohexadiene | None | 7 | Reflux | 24 | — | KKK | — | 8 |
| K ¹ | Cyclopentadiene | Benzene | 1 | 25 | 23 | — | F | 83 | 39 |
| L ¹ | 1-Vinylcyclopentene | — | — | — | — | — | 1:1 Adduct | — | 99 |
| N | 1-Vinylcyclohexene | — | — | — | — | — | 1:1 Adduct | — | 99 |
| O | 1-Vinylcycloheptene | — | — | — | — | — | 1:1 Adduct | — | 99 |
| T | 1-Vinylcyclooctene | — | — | — | — | — | 1:1 Adduct | — | 99 |
| T | 1,1'-Bicyclopentenyl | None | 1.8 | Reflux | 30 | seconds | U | 10 | 3 |
| T | 1,1'-Bicyclopentenyl | Butanol | — | Reflux | 5 | seconds | U | 54 | 20 |
| T | 1,1'-Bicyclohexenyl | None | 1.2 | Reflux | 30 | seconds | 1:1 Adduct | — | 3 |
| V | 1,1'-Dicyclohexenyl | — | — | — | — | — | 1:1 Adduct | 41-58.5 | 3, 10, 20 |
| Tetrachlorocyclopentadienone | Tetrachlorocyclopentadienone | — | — | — | — | — | Dimer | — | 68 |
| 3,4-Diphenylcyclopentadienone | 3,4-Diphenylcyclopentadienone | — | — | — | — | — | Dimer | — | 69 |
| 1,4-Dimethyl-2,3-diphenylcyclopentadienone | 1,4-Dimethyl-2,3-diphenylcyclopentadienone | — | — | — | — | — | LLL | — | 70 |
| Coumarin | 2,3-Dimethylbutadiene | Xylene | 2.1 | 260 | 40 | — | MMM | 22 | 70 |

¹ See p. 189 for explanation of symbols in this column.

¹ References 89-132 are listed on p. 192.

¹ A liquid.

¹ Probably XCIX or XCIXA p. 155.

¹ See p. 188 for explanation of symbols in this column.

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CHAPTER 4

PREPARATION OF AROMATIC FLUORINE COMPOUNDS FROM DIAZONIUM FLUOBORATES

THE SCHIEMANN REACTION

ARTHUR ROE

University of North Carolina

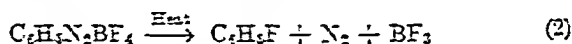
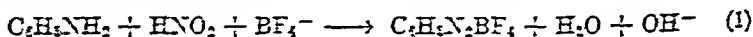
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INTRODUCTION

An excellent method for the introduction of fluorine into the aromatic nucleus, described by Balz and Schiemann¹ in 1927, has been extensively developed since that time by Schiemann. The method involves two steps: first, the preparation and isolation of a dry diazonium fluoborate; and second, the controlled decomposition of this salt by heat to yield an aromatic fluoride, nitrogen, and boron trifluoride.



The phenomenon which makes possible the Schiemann reaction is the remarkable stability of the dry diazonium fluoborates (sometimes called diazonium borofluorides). These salts, almost alone among the diazonium salts, are quite stable and insensitive to shock, and many can be handled safely in quantities of several kilograms. Most of them have definite decomposition temperatures, and the rates of decomposition, with few exceptions, are easily controlled. The over-all yields in general are satisfactory. No special apparatus is required, and the inorganic fluoborates necessary as intermediates may be purchased or easily prepared.

The first diazonium fluoborates were prepared in 1913 by Bart,² who made benzenediazonium fluoborate, as well as *p*-chloro-, *p*-nitro-, and *p*-ethoxy-benzenediazonium fluoborate. He noted the great stability of these compounds and claimed them to be useful as intermediates in preparing therapeutic agents and dyes; he did not prepare aromatic fluorides from them, however. No further report appeared until 1924 when Wilke-Dorfiert³ isolated two diazonium fluoborates and noted that they were less explosive than the diazonium perchlorates. In 1925

¹ Balz and Schiemann, *Ber.*, 60, 1185 (1927).

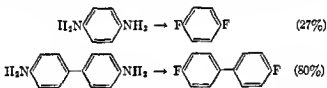
² Bart, *Gen. Pat.* 2,145,557 (*Chem.*, 9, 1569 (1915)).

³ Wilke-Dorfiert, *Z. organ. Chem.*, 37, 712 (1924).

Funk and Binder ⁴ published a study of the salts of fluoboric acid; they isolated benzenediazonium fluoborate and recorded some of its properties. Wilke-Dorfurt and Balz ⁵ in 1927 also isolated benzenediazonium fluoborate and reported the decomposition point of the salt to be 100°. Later the same year the paper of Balz and Schiemann ¹ appeared, showing that aromatic fluorides could be prepared in excellent yield by the decomposition of these dry diazonium fluoborates.

The Schiemann reaction may be carried out on a wide variety of amines, and over-all yields as high as 70% are not uncommon. Polynuclear aromatic compounds as well as benzene may be used; fluorine has been introduced into naphthalene, phenanthrene, anthracene, biphenyl, fluorene, and benzanthrone by this method. It has been shown that fluoropyridines and fluoroquinolines may be prepared in this manner.

The simultaneous introduction of two fluorine atoms by the use of a bis-diazonium fluoborate has been successful in several instances, although the yields are low unless the two diazonium groups are situated on different benzene rings.



The effect on the Schiemann reaction of other groups present in the ring is discussed in detail later in the sections "Preparation of Diazonium Fluoborates" and "Decomposition of Diazonium Fluoborates." At this point it need only be noted that the chief effect which other groups may have on the preparation of the intermediate diazonium fluoborate is to render the molecule more soluble, thus lowering the yield. The rate of decomposition of a diazonium fluoborate and the yield of fluoride obtained from it are profoundly affected by the presence of certain groups. Nitro groups generally cause unruly decomposition, and low yields of nitrofluorides result; other groups, such as alkoxy and amino, also lower the yield of fluoride obtained.

Diazonium fluoborates are occasionally used to introduce groups other than fluorine into an aromatic ring. For example, the diazonium fluoborate group may be replaced by the acetoxyl group,^{6,7} the nitro

⁴ Funk and Binder, *Z. anorg. allgem. Chem.*, **153**, 121 (1926).

⁵ Wilke-Dorfurt and Balz, *Ber.*, **60**, 115 (1927).

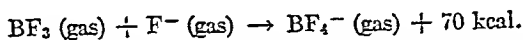
⁶ Smith and Haller, *J. Am. Chem. Soc.*, **61**, 143 (1939).

⁷ Haller and Schaffer, *J. Am. Chem. Soc.*, **55**, 4954 (1933).

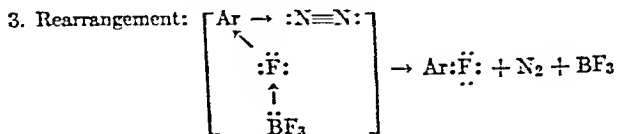
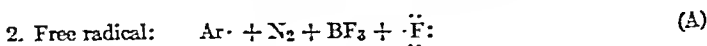
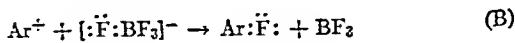
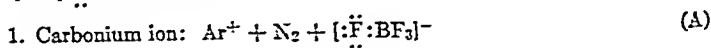
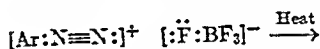
group,⁸ the nitrile group,⁹ and a hydrogen atom;^{10,11} an apparently unsuccessful effort has been made to replace it by a methoxyl group.¹² Diazonium fluoborates may also be used in the preparation of aromatic derivatives of arsenic,¹³ mercury,^{14,15} and copper.^{16,17}

MECHANISM OF THE REACTION

The mechanism of the decomposition of the diazonium fluoborates is not known with certainty, nor is the reason for the unusual stability of these salts fully understood. Schiemann^{1,18} proposed that the stability of these salts was due to the linking of an unstable diazonium cation with the complex fluoborate anion, the breaking down of the fluoborate complex to boron trifluoride and fluoride ion requiring approximately the same amount of energy as is given off by the decomposition of the cation. The amount of energy required was calculated by De Boer and Van Liempt¹⁹ to be about 70 kilocalories on the basis of the following equation.



There are three possible mechanisms for the decomposition of the diazonium fluoborates; they are shown diagrammatically below. In



⁸ Starkey, *Org. Syntheses, Coll. Vol. 2*, 225 (1943).

⁹ Ruggli and Caspar, *Helv. Chim. Acta*, **18**, 1414 (1935).

¹⁰ Leslie and Turner, *J. Chem. Soc.*, **1933**, 1590.

¹¹ Schmelkes and Rubin, *J. Am. Chem. Soc.*, **66**, 1631 (1944).

¹² Smith, Elisberg, and Sherrill, *J. Am. Chem. Soc.*, **68**, 1301 (1946).

¹³ Ruddy, Starkey, and Hartung, *J. Am. Chem. Soc.*, **64**, 828 (1942).

¹⁴ Dunker and Starkey, *J. Am. Chem. Soc.*, **61**, 3005 (1939).

¹⁵ Dunker, Starkey, and Jenkins, *J. Am. Chem. Soc.*, **58**, 2308 (1936).

¹⁶ Bolth, Whaley, and Starkey, *J. Am. Chem. Soc.*, **65**, 1455 (1943).

¹⁷ Whaley and Starkey, *J. Am. Chem. Soc.*, **68**, 793 (1946).

¹⁸ Schiemann, *Chem. Ztg.*, **52**, 754 (1925).

¹⁹ De Boer and Van Liempt, *Rec. trav. chim.*, **46**, 130 (1927).

order to make the formulas less complex, only those electrons immediately involved are represented; Ar represents any aromatic radical.

Hodgson, Birtwell, and Walker²⁰ propose mechanism 2, while Bell²¹ favors a mechanism like 1, although he calls it a "free radical" mechanism. Such evidence as there is does not make it possible to distinguish among these various possibilities. Bell conducted an interesting experiment to determine whether two "obstacle" amino groups in an optically active biphenyl molecule could be replaced by other groups without loss of optical activity. He reported that *lavo*-2,2'-diamino-6,6'-dimethylbiphenyl could be transformed into optically active 2,2'-diiodo-6,6'-dimethylbiphenyl by a diazonium reaction. The replacement of the amino groups by fluorine was also successful, but the optical activity of the product was so slight that Bell stated "the result was not regarded as unambiguous."



This evidence indicates that the replacement of the diazonium group by iodine and fluorine takes place by different mechanisms; this might be anticipated, as the one replacement occurs in cold aqueous solution and the other in the dry state at an elevated temperature. Racemization during the Schiemann reaction might be expected to take place with either mechanism 1 or 2, although it would be less likely with 3. Much work has been done on the mechanism of the decomposition of the diazonium salts in general,^{*} but little has been done directly with the fluoborates.

One related question upon which it is interesting to speculate is the connection between the relatively high stability of the diazonium fluoborates containing the nitro group (as evidenced by their high decomposition temperatures, which are as a group higher than those of any other substituted diazonium fluoborates; see Tables I, II, and III) and the uniformly low yields of nitrofluorides and high yields of tarry by-products obtained by the pyrolysis of these diazonium fluoborates.

Two possibilities suggest themselves. First, the known electron-attracting power of the nitro group may lessen the electron density around the diazonium group, thereby increasing its positive charge and

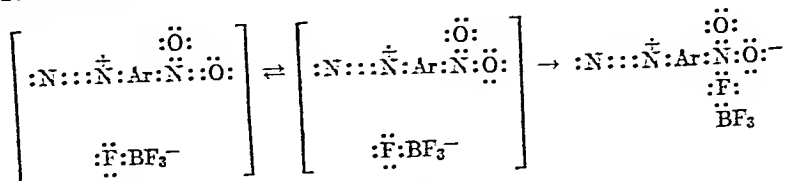
* For leading references see Waters, *J. Chem. Soc.*, 1942, 266, also reference 20.

²⁰ Hodgson, Birtwell, and Walker, *J. Chem. Soc.*, 1941, 770.

²¹ Bell, *J. Chem. Soc.*, 1934, 835.

increasing its electrostatic attraction for the fluoborate ion. This would tend to raise the decomposition point; why such a situation should lower the yield of the product on decomposition is not clear.

A second possibility (suggested in a private communication by Professor O. K. Rice) is that a coördinate bond could be formed between the fluoborate ion and the nitro group existing in one of its resonance forms. Such a situation would be expected to interfere with either mechanism



1 or 2, both of which require the presence of the BF_4^- ion close to the carbonium ion or free radical. Longer life of either the ion or radical postulated in mechanisms 1 and 2 would be expected from the above equation and would lead to increased polymerization and tar formation.

PREPARATION OF DIAZONIUM FLUOBORATES

Effect of Structure on the Yield of Diazonium Fluoborate

In general, any aromatic amine which can be diazotized will form a diazonium fluoborate, and yields above 90% are frequent. The yield reported is often of unpurified material, however, and may be high owing to coprecipitation of sodium fluoborate; a large excess of sodium fluoborate is sometimes used to obtain maximum yields, and some reported yields are over 100% for this reason.

The most important effect other groups in the ring may have upon the yield is that of increasing the solubility of the salt, thereby decreasing the yield. In a series of isomers, regardless of the nature of the second group, the *ortho* diazonium salt is usually the most soluble, hence is isolated in the lowest yield. The *para* isomer is usually formed in the highest amount, although the *meta* isomer is often formed in about the same yield.

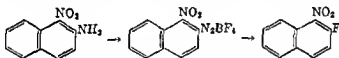
Certain groups, such as carboxyl and hydroxyl, tend to increase the solubility, and the transformation of these groups into esters and ethers improves the yield of the diazonium fluoborate. This is illustrated by the following facts. In an attempt to prepare the diazonium fluoborates from the three aminophenols, only the *meta* isomer was isolated, and this in less than 50% yield.² Starting with the phenetidines, however,

² Bennett, Brooks, and Glasstone, *J. Chem. Soc.*, 1935, 1821.

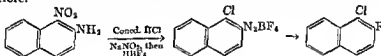
the diazonium fluoborates were isolated in the following yields: *ortho*, 69%; *meta*, 75%; *para*, 87%.¹³ The fluorophenetoles obtained may be converted to fluorophenols in good yields. The three anisidines were used with similar results. Again, the highest yield reported for the preparation of the diazonium fluoborate from *o*-aminobenzoic acid was 46%,¹³ whereas the yield from the corresponding ethyl ester was 80%.²⁴

No other generalizations concerning the effect of specific substituents on the yield of diazonium fluoborates can be made; the yield is also affected by the method of diazotization and the source of the fluoborate ion, as discussed in the next sections.

An interesting side reaction that may occur during the diazotization should be mentioned here. Willstaedt and Scheiber²⁴ attempted to prepare 1-nitro-2-fluoronaphthalene and found that their product would not undergo reduction to 1-amino-2-fluoronaphthalene; they attributed this to a powerful "*ortho* effect" exerted by the neighboring fluorine atom.



Schiemann and Ley²⁵ demonstrated that this was definitely not an *ortho* effect and showed that the reason for the non-reducibility of Willstaedt's nitro group was that no nitro group was present in the molecule. During the diazotization the nitro group was replaced by a chlorine atom; the final product was, therefore, 1-chloro-2-fluoronaphthalene. This replacement of a nitro group during diazotization has been observed before.²⁶



Methods of Preparation

In preparing diazonium fluoborates the volume of solution is kept as small as possible to reduce loss of product, since the salts are slightly soluble even in cold water. The salts must be thoroughly dried, as unruly decomposition and lowered yields result from the pyrolysis of a moist product. Sometimes the fluoborates undergo spontaneous de-

¹³ Bergmann, Engel, and Sandor, *Z. physik. Chem.*, **10B**, 106 (1930).

²⁴ Willstaedt and Scheiber, *Ber.*, **67**, 466 (1934).

²⁵ Schiemann and Ley, *Ber.*, **69**, 960 (1936).

²⁶ Morgan, *J. Chem. Soc.*, **81**, 1376 (1902).

composition if a tightly packed moist salt is allowed to stand. Rapid drying is advantageous; this can be achieved by spreading the salt rather thinly on porous paper (supported on a screen or wire netting so that air can circulate freely underneath) and placing near a hood. Direct sunlight is reported to cause decomposition of fluoborates.⁷⁷ Occasionally some diazonium fluoborates will decompose while drying; *m*-methoxybenzenediazonium fluoborate is quite unstable,^{23, 25, 29} and *o*-methylbenzenediazonium fluoborate sometimes gives trouble in this way. Diazonium fluoborates of certain heterocyclic compounds are likewise unstable.^{31, 32}

There are two general methods of preparing these salts. The first method involves the diazotization of the amine in the usual manner, followed by addition of the fluoborate ion in the form of fluoboric acid or some derivative. In the second method the amine is diazotized in the presence of the fluoborate ion, and the diazonium fluoborate precipitates continuously as the diazotization proceeds. Various modifications of these procedures are described in detail below.

I. Diazotization Followed by Addition of Fluoborate Ion

| DIAZOTIZING AGENT | SOURCE OF FLUOBORATE ION |
|--|--------------------------|
| A. Nitrous acid | Fluoboric acid |
| B. Nitrous acid | Sodium fluoborate |
| C. Nitrous acid | Ammonium fluoborate |
| D. Amyl nitrite | Fluoboric acid |
| E. Nitrosylsulfuric acid | Fluoboric acid |
| F. Nitrous acid in presence of hydrofluoric acid | Boron trifluoride |

Methods IA, B, and C. The most common procedure in following the first method consists in diazotizing as usual with sodium nitrite and hydrochloric acid,* and adding a cold aqueous solution of fluoboric acid, sodium fluoborate, or ammonium fluoborate to the clear diazonium solution (filtered if necessary). A precipitate forms immediately and is allowed to stand at 0° or lower for at least half an hour to ensure complete precipitation. The precipitate is then filtered, washed with cold water (or cold sodium fluoborate solution or fluoboric acid), sucked as

* Bradlow and VanderWerf (private communication) report that considerable time may be saved when diazotizing large quantities by adding solid sodium nitrite in small portions to a vigorously stirred solution which is kept below 0° by the addition of Dry Ice.

²³ Schiemann, *J. prakt. Chem.*, [2] 140, 97 (1934).

²⁵ Becker and Adams, *J. Am. Chem. Soc.*, 54, 2973 (1932).

²⁹ Schiemann, *Z. physik. Chem.*, A156, 397 (1931).

³¹ Bradlow and VanderWerf, *J. Am. Chem. Soc.*, 70, 654 (1948).

³² Roe and Hawkins, *J. Am. Chem. Soc.*, 69, 2443 (1947).

⁷⁷ Roe and Hawkins, New York Meeting A.C.S., 1947, *Abstracts*, p. 36L.

dry as possible on the filter, then sometimes washed with cold alcohol, dioxane, or ether. Many fluoborates are appreciably soluble in alcohol or dioxane, however, so caution in washing is necessary. If a clear diazonium solution is used and the precipitate dried rapidly as described above, washing with organic solvents is unnecessary. Drying the salt in a desiccator is usually not required. Many fluoborates are sufficiently stable to be recrystallized from acetone, and some may be recrystallized from water; in this way very pure salts can be prepared if needed.

It is advisable to filter the solution (or extract it with ether) before addition of the fluoborate ion in order to remove by-products formed during the diazotization; the presence of these by-products in the diazonium fluoborate is undesirable and lowers the yield of final product. The formation of these by-products—chiefly phenols and coupling products—seems to be decreased when the diazotization is carried out in the presence of the fluoborate ion, as in method II.

Meigs²² states that the yields are lowered when fluoborate ion is added to the diazonium chloride in strongly acid solution because of the increased solubility of the diazonium fluoborate in such a solution; it is recommended that the solution contain less than 1 mole of hydrogen ion per liter at the time the fluoborate is added. Sodium fluoborate rather than fluoboric acid is recommended as a source of the fluoborate ion. Support for this recommendation was obtained by adding four different precipitants to four identical solutions each containing 0.1 mole of benzenediazonium chloride. The results are shown below.

| PRECIPITANT (IN SOLUTION) | HYDROGEN ION IN MOLES PER LITER AT END | YIELD % |
|--|--|------------|
| 1. 0.11 mole HBF_4 | 1.96 | 67 |
| 2. 0.11 mole 50% HBF_4 50% NaBF_4 | 1.09 | 78.1 |
| 3. 0.11 mole 25% HBF_4 75% NaBF_4 | 0.67 | 80.1 |
| 4. 0.11 mole NaBF_4 | 0.26 | 84.3 |

Dippy and Williams²³ reported similar findings in the preparation of *o*-fluorobenzoic acid; *o*-carbethoxybenzenediazonium fluoborate was prepared by the addition of fluoboric acid to the diazonium chloride; an excess of acid lowered the yield appreciably.

Finger and Reed²⁴ carried out parallel experiments using both sodium and ammonium fluoborate as the source of fluoborate ion; they found

²² Meigs, U. S. pat. 1,916,327 [*C.A.*, **27**, 4539 (1933)].

²³ Dippy and Williams, *J. Chem. Soc.*, 1934, 1466.

²⁴ Finger and Reed, *Trans. Illinois State Acad. Sci.*, **33**, No. 2, 108 (1940) [*C.A.*, **35**, 2450 (1941)].

that in most experiments the two salts gave practically identical results. Sodium fluoborate is more soluble than the ammonium salt, and a larger volume of water is therefore necessary if the latter is used.

Method ID. von Braun and Rudolph²² used amyl nitrite followed by the addition of 2 moles of fluoboric acid in the preparation of 2-nitro-6-methylbenzenediazonium fluoborate from the amine in 50% yield. This method was also used by Willstaedt and Scheiber²⁴ in the preparation of 1-benzeneazo-2-naphthalenediazonium fluoborate in 31% yield from the amine.

Method IE. Nitrosylsulfuric acid was used as the diazotizing agent in the preparation of the diazonium sulfate of Bz-1-aminobenzanthrone by Lüttringhaus and Neresheimer;²⁵ the slightly soluble diazonium sulfate was dissolved in warm water and converted quantitatively to the fluoborate by addition of fluoboric acid.

Method IF. The use of boron trifluoride in the preparation of the diazonium fluoborates is described by Meigs.²³ The diazotization is carried out in the presence of hydrofluoric acid, then gaseous boron trifluoride is led into the solution until precipitation of the diazonium fluoborate is complete.

An excellent method of analyzing diazonium fluoborates by decomposing them in sulfuric acid and measuring the nitrogen evolved has been reported by Schiemann and Pillarsky.²³

EXPERIMENTAL PROCEDURES METHOD I. Almost any diazonium fluoborate may be prepared by any of the procedures in this or the next section. The preparation of benzenediazonium fluoborate,²² *p*-carbethoxybenzenediazonium fluoborate,²² and 4,4'-biphenyl-*bis*-diazonium fluoborate⁴¹ by method I is described in *Organic Syntheses*; the preparation of *p*-nitrobenzenediazonium fluoborate by method II is also described there.⁸ All the experimental procedures in this chapter have been checked by the author.

Preparation of Reagents. Fluoboric acid and sodium and ammonium fluoborate are available commercially. The preparation of the first two is briefly described.

Fluoboric acid may be prepared by dissolving 1 mole of boric acid slowly with cooling in approximately 4 moles of 40–48% hydrofluoric acid. The mixing should be done in a wax-lined or rubber beaker, and the temperature should be kept below 25° to prevent melting of the

²² von Braun and Rudolph, *Ber.*, **64**, 2465 (1931).

²³ Lüttringhaus and Neresheimer, *Ann.*, **473**, 259 (1929).

²⁴ Schiemann and Pillarsky, *Ber.*, **62**, 3035 (1929).

²⁵ Flood, *Org. Syntheses, Coll. Vol. 2*, 295 (1943).

⁴⁰ Schiemann and Winkelmüller, *Org. Syntheses, Coll. Vol. 2*, 299 (1943).

⁴¹ Schiemann and Winkelmüller, *Org. Syntheses, Coll. Vol. 2*, 188 (1943).

wax by the heat of reaction. Stirring may be done with a lead or rubber rod.

Sodium fluoborate⁴ may be prepared by adding 333 g. of powdered boric acid to 1338 ml. of concentrated hydrochloric acid. To this mixture 900 g. of sodium fluoride is added slowly with shaking and cooling. The mixture is allowed to stand for two hours and filtered. About 1465 ml. of solution is obtained, containing 5.38 moles of sodium fluoborate.

p-Bromobenzenediazonium Fluoborate. To a mixture of 62 ml. (0.75 mole) of concentrated hydrochloric acid and an equal amount of water is added 43 g. (0.25 mole) of *p*-bromoaniline. The mixture is cooled to 0°, and a cold solution of 17.3 g. (0.25 mole) of sodium nitrite is added slowly, the temperature being kept near 0°; Dry Ice added in small portions to the solution is helpful in controlling the temperature. The diazotized solution is filtered if necessary through a cold sintered-glass filter; a cold solution of 35 g. (0.34 mole) of ammonium fluoborate in 120 ml. of water is added with vigorous stirring. The light-green precipitate is stirred at 0° for at least half an hour, filtered, and washed with 25 ml. of cold 5% ammonium fluoborate solution, 30 ml. of ice-cold methanol, and several 50-ml. portions of ether, the precipitate being sucked as dry as possible after each washing. The salt is dried by spreading it thinly on porous paper supported on a screen or wire netting allowing air circulation underneath. The yield is 48–55 g. (71–82%).

m-Nitrobenzenediazonium Fluoborate. This compound may be prepared by following the above directions, using 34.6 g. (0.25 mole) of *m*-nitroaniline. A solution of 35 g. of either sodium fluoborate or ammonium fluoborate in water may be used as a precipitant, or, if preferred, 48 ml. of cold 42% fluoboric acid (0.3 mole). The precipitate is treated as described above. The yield is 53–57 g. (90–97%).

β-Naphthalenediazonium Fluoborate. This salt may be prepared by the method described for *p*-bromobenzenediazonium fluoborate, using 35.8 g. (0.25 mole) of *β*-naphthylamine. Dioxane may be substituted for methanol for washing the precipitate. The yield is 55–60 g. (90–97%).

m-Toluenediazonium Fluoborate. The apparatus is placed in a good hood. A wax-coated beaker is placed in an ice-salt bath; 41 ml. of concentrated hydrochloric acid and 12 g. of 48% hydrofluoric acid are placed in the beaker, and 26.8 g. (0.25 mole) of freshly distilled *m*-toluidine is added. The solution is diazotized with a cold solution of 17.3 g. of sodium nitrite, the temperature being kept at about 0°; a wax-coated or lead stirrer is used. When all the sodium nitrite has been added, boron trifluoride from a cylinder is introduced until precipitation of the

⁴ Suter, Lawson, and Smith, *J. Am. Chem. Soc.*, **61**, 161 (1939).

diazonium fluoborate is complete. Efficient stirring and cooling are essential during the addition of the boron trifluoride; Dry Ice added to the solution helps control the temperature. The precipitate is washed with 50 ml. of ice water and 50 ml. of iced methanol, followed by several washings with ether; it is then dried as described above. The yield is 39–43 g. (76–84%). This is the least convenient of any of the procedures for the preparation of a diazonium fluoborate on a laboratory scale.

II. Diazotization in the Presence of Fluoborate Ion

Source of the fluoborate ion:

- A. Fluoboric acid.
- B. Sodium fluoborate.
- C. Ammonium fluoborate.
- D. Nitrosyl fluoborate.

Excellent yields are obtained by diazotizing in the presence of fluoborate ion. Fluoboric acid may be the only acid present, acting both as acid and source of fluoborate ion. Sodium and ammonium fluoborates are used in conjunction with an acid (usually hydrochloric), as is nitrosyl fluoborate, although the last serves as diazotizing agent as well as a source of fluoborate ion.

The insoluble diazonium fluoborate separates from the solution as it is formed; side reactions such as phenol formation and coupling are held to the minimum. Temperature control is not so critical in this procedure; the temperature may in some cases rise to 30° during the diazotization with no ill effect.²² There are certain disadvantages, however; a continuously thickening precipitate is formed as the reaction proceeds; efficient stirring overcomes this difficulty. The fumes of fluoboric acid are corrosive and obnoxious, and fluoboric acid has been known to eat its way out of the wax-lined bottles in which it is stored. The yields of diazonium fluoborates produced by this method are usually as good as and sometimes better than the yields by method I; it is claimed²² that a cleaner and more easily purified salt results from method II.

Method IIA. Starkey² prepared *p*-nitrobenzenediazonium fluoborate in 95–99% yield from *p*-nitroaniline with fluoboric acid as the only acid present. Aniline, *o*-, *m*-, and *p*-chloroaniline, ethyl *p*-aminobenzoate, *p*-aminoacetophenone, and other amines have been converted to the diazonium fluoborates by this method in better yield than by other methods.²³ These are but a few examples of the preparation of diazonium fluoborates by diazotization in the presence of fluoboric acid.

The tetrazotization of diamines is also carried out with good yields this way; Ruggli and Caspar⁹ report the preparation of 1,4-benzene-bis-diazonium fluoborate from *p*-phenylenediamine in 78% yield, varying the method slightly by adding a mixture of the amine and sodium nitrite slowly to a cold solution of fluoboric acid. The corresponding *meta* derivative is formed in an unspecified lower yield. They also prepared 1,5-dimethyl-2,4-benzene-bis-diazonium fluoborate quantitatively by this method.

Methods IIB and C. Parts¹⁰ diazotized β -naphthylamine in the presence of sodium fluoborate to prepare the diazonium fluoborate in unspecified yield. Both sodium and ammonium fluoborates are now available commercially, and there is no reason why they could not be used in the preparation of diazonium fluoborates in this way.

Method IID. Voznesenkii and Kurskii¹¹ prepared benzenediazonium fluoborate in 90% yield from aniline hydrochloride and nitrosyl fluoborate. The latter reagent was prepared from fluoboric acid and nitrogen dioxide in good yield.

EXPERIMENTAL PROCEDURES METHOD II. The preparation of *p*-nitrobenzenediazonium fluoborate is described in *Organic Syntheses*.⁹ Any amino which can be diazotized, including diamines, may be transformed into the diazonium fluoborate by this method.

***p*-Methoxybenzenediazonium Fluoborate.** To 100 ml. of 42% fluoboric acid (0.625 mole) diluted with 100 ml. of water is added 30.8 g. of *p*-anisidine (0.25 mole); the solution is cooled in an ice bath. A solution of 17.3 g. of sodium nitrite (0.25 mole) in 35 ml. of water is added slowly, the temperature being kept at about 10°. The gradually thickening precipitate requires vigorous stirring toward the end of the reaction. The mixture is cooled to 0° and filtered. The precipitate is washed with 40 ml. of cold 5% fluoboric acid, 50 ml. of ice-cold methanol, and several 50-ml. portions of ether, and dried overnight as described in Method I. The yield is 52–54 g. (94–98%).

Instead of fluoboric acid, 51 ml. of concentrated hydrochloric acid, 100 ml. of water, and 35 g. of either sodium or ammonium fluoborate may be used. The procedure is identical with the above, and the yield is about the same.

4,4'-Biphenyl-bis-diazonium Fluoborate. This salt may be prepared by the same procedure as described above, using 46 g. (0.25 mole) of benzidine and 240 ml. of 42% fluoboric acid. If desired, 64.4 g. (0.25 mole) of benzidine dihydrochloride may be added to 91 ml. (0.57

⁹ Parts, *Z. physik. Chem.*, **10B**, 264 (1930).

¹¹ Voznesenkii and Kurskii, *J. Gen. Chem. U.S.S.R.*, **8**, 524 (1938) [*C.A.*, **32**, 8379 (1938)].

mole) of fluoboric acid and 250 ml. of water; this is then diazotized as above. The yield is 80–86 g. (93–100%).

3-Pyridinediazonium Fluoborate.³¹ Twelve and a half grams of 3-aminopyridine is dissolved in a mixture of 50 ml. of 40% fluoboric acid and 100 ml. of 95% ethanol. The solution is cooled to 0°, and a stream of ethyl nitrite⁴⁵ is passed in until precipitation of the diazonium fluoborate is complete. Fifty milliliters of cold ether is added to complete the precipitation, and the mixture is filtered while cold and washed once with cold ether and then once with cold petroleum ether. The precipitate must not be allowed to become dry at any time, for this diazonium salt when dry will undergo violent spontaneous decomposition. The salt is dampened with petroleum ether and transferred to a beaker containing 50 ml. of ice-cold high-boiling petroleum ether.

DECOMPOSITION OF DIAZONIUM FLUOBORATES

Effect of Structure on the Decomposition of Diazonium Fluoborates

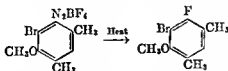


The decomposition of diazonium fluoborates usually proceeds smoothly, and the average yield from all types of compounds is in the neighborhood of 65%. There is no great variation in the yield of *ortho*, *meta*, and *para* isomers formed by the decomposition of substituted diazonium fluoborates, although in general the *ortho* isomer is formed in the smallest amount. Polynuclear aromatic compounds decompose smoothly and produce the fluorine compounds in good yields. Of the few heterocyclic diazonium fluoborates known, some decompose spontaneously, while others are quite stable and decompose evenly, producing good yields of the fluoride. Decomposition of substances containing two diazonium fluoborate groups occurs smoothly and in surprisingly good yield if the groups are on different rings of a polynuclear molecule; otherwise the yields are low.

Diazonium fluoborates of otherwise unsubstituted aromatic molecules give the best yield of fluorides; however, the presence of halogen⁴⁶ and alkyl groups on the molecule does not seriously interfere with the yield. Compounds with an ether linkage decompose smoothly but the yields are somewhat lowered, most of them being between 40% and 60%. The presence of ester, carboxyl, amino, nitro, and hydroxyl groups also lowers the yield, the effect increasing roughly in the order named. The above statements are generalizations, and some individual exceptions may be found.

⁴⁵ Semon and Damerell, *Org. Syntheses, Coll. Vol. 2*, 204 (1943).

Highly substituted molecules do not necessarily give poor yields, as evidenced by the 74% yield of 2-bromo-3-methoxy-4,6-dimethylfluorobenzene obtained by the decomposition of the corresponding diazonium fluoborate.²⁸



The compounds whose decomposition is most troublesome and difficult to control are those containing the nitro group. The decomposition of these compounds is tempestuous and unruly, and special methods are required for handling them, as outlined in a later section. The yields of fluoronitro compounds are, with few exceptions, low; the preparation of 2-fluoro-6-nitrotoluene in 63% yield from the corresponding diazonium fluoborate⁴⁶ and the preparation of fluoronitromesitylene in an over-all yield of 65-68% from the amine⁴⁷ are the best yields of nitrofluoro compounds yet reported. The following list serves to illustrate the generalizations in the previous paragraphs by showing the yields obtained by the decomposition of a few simple *ortho*- and *para*-substituted benzenediazonium fluoborates; in every case the best reported yield is given. (References are to be found in the larger tables at the end of the chapter and are not repeated here.)

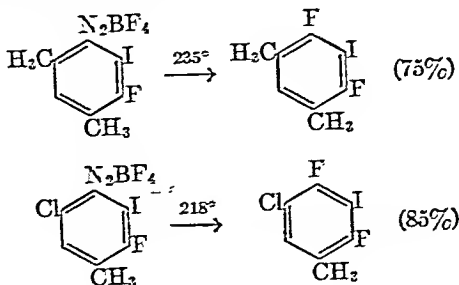
| Ortho SUBSTITUENT | YIELD FLUORIDE | Para SUBSTITUENT | YIELD FLUORIDE |
|---|-------------------|--|-------------------|
| | % | | % |
| H— | 100 | H— | 100 |
| CH ₃ — | 90 | CH ₃ — | 97 |
| C ₂ H ₅ O ₂ C— | 87 | C ₂ H ₅ O ₂ C— | 90 |
| Cl— | 85 | Br— | 75 |
| Br— | 81 | CH ₃ O— | 67 |
| I— | 70 | F— | 62 |
| CH ₃ O— | 67 | O ₂ N— | 63 |
| CH ₃ O ₂ C— | 53 | C ₂ H ₅ O— | 53 |
| C ₂ H ₅ O— | 36 | (C ₂ H ₅) ₂ N— | 20 |
| F— | 36 | (CH ₃) ₂ N— | 17 |
| HO ₂ C— | 19 | | |
| O ₂ N— | 19 | | |

The statement has been made²⁷ that the yield of fluoride is somewhat dependent upon the decomposition temperature of the diazonium fluo-

⁴⁶ Lock, *Ber.*, 69, 2253 (1936).

⁴⁷ Finger and co-workers, Atlantic City Meeting A.C.S., 1946, *Abstracts*, p. 13M.

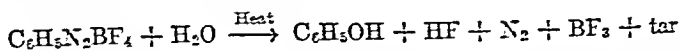
borate, lower temperatures producing better yields. This statement is qualitatively true for unsubstituted hydrocarbons and those already containing one or more fluorine atoms; for other types of diazonium fluoborates the relationship does not hold very well. The two reactions which follow illustrate this statement.



The decomposition temperature of 2-iodo-3-fluoro-4,6-dimethylbenzenediazonium fluoborate (235°) is the highest reported in the literature.

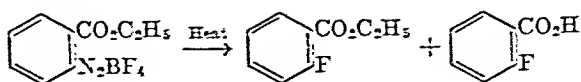
Side Reactions during Decomposition

The diazonium fluoborate must be thoroughly dry before being decomposed. The presence of moisture sometimes makes the decomposition uncontrollable and always markedly lowers the yield; phenols and tars are formed instead of the desired product. However, perfectly dry

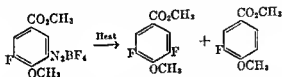


fluoborates sometimes form tar and resinous material on decomposition. The ability of boron trifluoride to bring about condensations and polymerizations is well known, and this action is probably responsible in large measure for the formation of these products of high molecular weight. The decomposition of molecules containing the nitro group always results in the formation of a large amount of tarry material of unknown nature.

The boron trifluoride evolved during the decomposition may cause splitting of ester groups present on the molecule. Schiemann² and Bergmann, Engel, and Sandor³ report that some *o*-fluorobenzoic acid is formed directly during the decomposition of *o*-carbethoxybenzene-diazonium fluoborate.



The substitution of hydrogen for the diazonium fluoborate radical during pyrolysis was reported by Niemann, Benson, and Mead⁴³ (also private communication from Dr. Niemann). They prepared methyl 3,5-difluoro-4-methoxybenzoate from 2-methoxy-3-fluoro-5-carbomethoxybenzenediazonium fluoborate, obtaining at the same time some methyl 3-fluoro-4-methoxybenzoate. Never more than one-fifth as much monofluoro as difluoro compound was formed, and the yield of the crude ester mixture was only about 35%. A somewhat similar



result was reported by Schmelkes and Rubin.⁴⁴ They prepared 2-fluoro-4-nitrotoluene and found that, if all the methanol used in washing the diazonium fluoborate was not carefully removed, partial deamination with formation of 4-nitrotoluene occurred on pyrolysis of the salt. Of interest in connection with the two results reported above is the work of Leslie and Turner,⁴⁵ who obtained a 78% yield of 2-nitro-3'-bromobiphenyl from 2-nitro-3'-bromo-4,4'-biphenyl-bis-diazonium fluoborate by warming it with ethanolic sulfuric acid.

Apparatus for Decomposing Diazonium Fluoborates

Large amounts of boron trifluoride and nitrogen are evolved during the reaction; wide tubing should be used for all connections. The apparatus should be arranged so that these gases may be led to a good hood; often a trap to catch the boron trifluoride is included. The boron trifluoride may be taken up in water, alkali, or a suspension of sodium fluoride in water; the latter procedure is recommended as a satisfactory method of preserving the gas for future use, as sodium fluoborate is formed.³³

The apparatus depends on the method of decomposition chosen and upon the volatility of the product. The flask in which the decomposition is carried out should never be more than half full of the salt. If the product is relatively non-volatile, as are many of the biphenyl derivatives, a short air condenser attached to the decomposition flask will suffice.⁴² Another satisfactory method of decomposing compounds of this type is to carry out the decomposition in a large distilling flask, the side arm

⁴³ Niemann, Benson, and Mead, *J. Am. Chem. Soc.*, **63**, 2204 (1941).

⁴⁴ Shaw and Turner, *J. Chem. Soc.*, 1932, 509.

of which leads to another distilling flask acting as a receiver; the receiver may be cooled with running water if necessary.⁴¹ More volatile products, such as the fluorotoluenes, will distil during the decomposition, and an efficient cooling system consisting of a condenser, cooled receiving flask, and an ice trap must be provided. Some compounds, such as the fluoro-benzotrifluorides, are still more volatile, and special brine or Dry Ice traps are necessary.^{50, 51}

Methods of Decomposing Diazonium Fluoborates

The pyrolysis is carried out by heating the *dry* diazonium fluoborate gently near its surface until decomposition commences. Often no more heat is required, the decomposition continuing spontaneously; sometimes heat must be applied intermittently. Occasionally the reaction becomes too violent and the flask must be cooled with water or by rubbing it with ice. After most of the salt has decomposed, the flask is heated strongly to ensure complete decomposition of the salt.

Most decompositions go smoothly, and large quantities of material may be handled safely.³⁹ Compounds containing the nitro group are an outstanding exception; they usually decompose suddenly and with considerable violence. Usually they are mixed with three to five times their weight of a diluent, such as sand, barium sulfate, or sodium fluoride,⁵² and decomposed in small quantities—5 g. to 25 g. at a time. Carrying out the decomposition at a reduced pressure often helps control the reaction.

The diazonium fluoborates may be decomposed in the following ways:

A. By heating the salt gently with a free flame in a flask fitted with a suitable condensing system to collect the product.

B. Same as A, the decomposition being carried out under reduced pressure.

C. By placing the salt in a flask and keeping it for some time at a temperature 10–20° below its decomposition temperature.^{53, 54}

D. By adding the salt little by little to a flask whose temperature is at or above the decomposition temperature of the salt.^{53, 54}

E. By mixing a few grams of the salt with three or four times its weight of a diluent such as sand, barium sulfate, or sodium fluoride, and decomposing the mixture according to one of the above methods.^{14, 33, 52}

⁵⁰ Aclony, *J. Am. Chem. Soc.*, **56**, 2063 (1934).

⁵¹ Finger and Reed, *J. Am. Chem. Soc.*, **66**, 1972 (1944).

⁵² Roe and Fleishmann, *J. Am. Chem. Soc.*, **69**, 509 (1947).

⁵³ Cannoni de Degiorgi and Zappi, *Anales asoc. quim. argentina*, **28**, 72 (1940) [*C.A.*, **34**, 6593 (1940)].

⁵⁴ Kleiderer and Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

F. By suspending the salt in an indifferent solvent such as petroleum ether, toluene, biphenyl, or quinoline, and heating.^{27, 31, 45, 56}

Method A is the one most often employed, although Method F is used occasionally. The other techniques are used chiefly for carrying out the decomposition of diazonium fluoborates containing the nitro group.

Experimental Procedures

The amount of diazonium fluoborates used in the following examples is the amount prepared in the previous experimental section. In every preparation except that of *m*-nitrofluorobenzene, much larger quantities may be used safely.

***m*-Fluorotoluene.** Forty grams of dry *m*-toluenediazonium fluoborate is placed in a 500-ml. round-bottomed flask connected by a wide tube through a condenser to two 500-ml. Erlenmeyer flasks in series cooled in ice-salt mixtures. The last flask is fitted with a tube leading to a good hood or to an absorption flask containing ice and water, soda solution, or a suspension of sodium fluoride to absorb the voluminous fumes of boron trifluoride evolved; the outlet tube from the last flask should lead to a hood. The salt is heated gently with a free flame at a point near the surface until decomposition commences as evidenced by the evolution of white fumes; the flame is then removed. Gentle heating is continued only if necessary to keep the decomposition going; at the end of the decomposition the flask is heated vigorously until no more fumes are evolved. The fluorotoluene may be removed completely from the decomposition flask by further heating and the application of slight suction; another satisfactory procedure is to return all the fluorotoluene to the reaction flask, add water to dissolve the boron trifluoride and hydrogen fluoride, and steam-distil. In either procedure the fluorotoluene is dissolved in 150 ml. of ether, washed first with dilute sodium hydroxide, then with water, and dried over calcium chloride. After removal of the ether the product boils at 114–115°; yield, 19 g. (89%).

***p*-Fluoroanisole.** A 500-ml. round-bottomed flask is connected by a wide tube through a condenser to a cooled 250-ml. distilling flask, the side arm of which leads to a hood or trap as described above. The dry *p*-methoxybenzenediazonium fluoborate (51 g.) is placed in the decomposition flask, and the decomposition is carried out as described above. The small amount of product in the receiving flask is returned to the decomposition flask and steam-distilled. The distillate is extracted with 100 ml. of ether; the ether solution is washed with 50 ml. of 10%

²⁷ Goldberg, Ordas, and Carsch, *J. Am. Chem. Soc.*, **69**, 260 (1947).

⁵⁶ Zenitz and Hartung, *J. Org. Chem.*, **11**, 444 (1946).

sodium hydroxide solution, followed by water, and dried over calcium chloride. After removal of the ether on the steam bath the product boils at 156–157°; yield, about 16 g. (52%).

p-Bromofluorobenzene. The dry *p*-bromobenzenediazonium fluoborate (50 g.) is placed in the decomposition flask of an apparatus similar to that described above for the preparation of *p*-fluoroanisole. The decomposition of the salt and the working up of the product are carried out as described for *p*-fluoroanisole. The product boils at 150–151°; yield, 25 g. (77%).

β -Fluoronaphthalene. The apparatus consists of a 500-ml. distilling flask whose side arm leads to another distilling flask of the same size which is cooled with running water. The side arm of the receiving flask leads to a good hood or a trap as described above. The dry β -naphthalenediazonium fluoborate (55 g.) is placed in the decomposition flask and heated gently until decomposition starts; further gentle heating may be necessary from time to time. Some of the white powdery product is collected in the receiving flask; at the conclusion of the decomposition the product is steam-distilled. The product melts at 60°, and the yield is about 27 g. (81%).

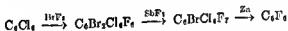
4,4'-Difluorobiphenyl. The apparatus is identical with that described for β -fluoronaphthalene; 80 g. of dry 4,4'-biphenyl-bis-diazonium fluoborate is placed in the decomposition flask, and the decomposition is carried out as described for β -fluoronaphthalene. The product is steam-distilled; yield, 36 g. (82%). A second steam distillation is sometimes necessary to obtain a pure product, m.p. 99°.

m-Fluoronitrobenzene. The apparatus consists of a 250-ml. flask connected by a wide bent tube through a water-cooled condenser to a second 250-ml. flask acting as a receiver. The side arm of the flask leads to a good hood or a trap as previously described. An intimate mixture of 13 g. of *m*-nitrobenzenediazonium fluoborate and 36 g. of clean dry sand (or barium sulfate or sodium fluoride) is placed in the reaction flask and heated cautiously until decomposition starts. Intermittent heating is necessary to complete the reaction. The products of four such decompositions are combined in a 1-l. flask and steam-distilled. The product is taken up in 100 ml. of ether, washed with 25 ml. of 5% sodium hydroxide then twice with 25 ml. of water, and dried over anhydrous potassium carbonate. After removal of the ether on a steam bath the product distills at 53–54°/1–2 mm.; the yield is 16 g. (54%). It is possible to decompose as much as 25 g. of the salt at a time, although the yields are sometimes smaller with larger quantities.

3-Fluoropyridine. The 3-pyridinediazonium fluoborate,* covered with at least 50 ml. of cold high-boiling petroleum ether, is allowed to warm slowly until decomposition starts; the temperature is kept below 25°, however, as the decomposition is uncontrollable above this temperature. After decomposition is complete, 5 ml. of concentrated hydrochloric acid is added to ensure salt formation, and the solvent is removed under reduced pressure. The residue is made alkaline with sodium hydroxide solution, the solution being kept cold during the process. The solution is then distilled; solid sodium hydroxide is added to the distillate, whereupon an oil separates. The oil, after drying over sodium hydroxide, distills at 105–107°/752 mm.; the yield is 6.4 g. (50% from the amine). The use of ether to extract the product is impractical because of the difficulty in separating the ether from the product.

OTHER METHODS OF PREPARING AROMATIC FLUORIDES

During World War II a vast amount of research was done on the preparation of organic fluorine compounds; few aromatic fluorocarbons were prepared, however. Perfluoro alicyclic compounds (such as dodecafluorocyclohexane) were prepared by direct fluorination of aromatic hydrocarbons in the presence of a catalyst consisting of copper coated with the fluorides of silver³⁷ and by fluorination with cobalt trifluoride,³⁸ silver difluoride,³⁹ and other metallic fluorides.⁴⁰ All compounds prepared by any of these methods are fully saturated. The preparation of two aromatic fluorides—hexafluorobenzene and octafluorotoluene—has been accomplished;⁴¹ the method is illustrated in the accompanying



equation. No simple hydrogen-containing aromatic fluorine compounds have been prepared by any of the above methods.

Much work had been done on direct fluorination before the war, and it had been found that direct fluorination of aromatic compounds is difficult because of the extreme activity of this halogen; instead of undergoing fluorination many compounds are decomposed, polymerized,

* 3-Pyridinediazonium fluoborate undergoes violent spontaneous decomposition when dry. Consequently the material, prepared as described on p. 200 and covered with petroleum ether, is used directly without drying and weighing.

³⁷ Cady, Grosse, Barber, Burger, and Shellen, *Ind. Eng. Chem.*, **39**, 200 (1947).

³⁸ Fowler and co-workers, *Ind. Eng. Chem.*, **39**, 293 (1947).

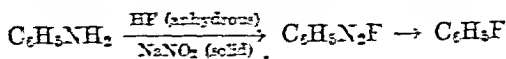
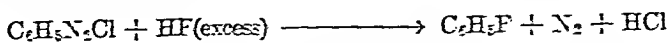
³⁹ Fowler and Heckel, *Ind. Eng. Chem.*, **39**, 340 (1947).

⁴⁰ Fowler and co-workers, *Ind. Eng. Chem.*, **39**, 313 (1947).

⁴¹ Melroe, Lindgren, and Ugoth, *Ind. Eng. Chem.*, **39**, 378 (1947).

or transformed into saturated cyclic fluorides by the action of fluorine.⁶²⁻⁶⁷ Few well-defined products have been reported, though several patents covering this field have been issued, a few of which are noted here.⁷³⁻⁷⁵

A method of preparing aromatic fluorine compounds that has had considerable success is the decomposition of diazonium salts in hydrogen fluoride, aqueous or anhydrous.⁷³⁻⁷⁷ The first aromatic fluorine com-



pound prepared, *p*-fluorobenzoic acid, was made this way by Schmitt and von Gehren^{83,84} in 1870. This method has the disadvantage of requiring special apparatus capable of handling hydrofluoric acid. Yields are often excellent, however, and a few compounds for which the Schiemann reaction would not work have been made this way; one of these is 2-iodo-3-fluorobenzoic acid.⁸⁵

The method devised by Wallach^{82,84} has had limited usefulness. It consists of isolating a diazonium piperidide and decomposing it with aqueous hydrogen fluoride. The intermediates, in contrast to the diazonium fluoroborates, are unstable and difficult to purify, and they can be handled safely only in small quantities; the yields are generally low. This method has not been much used since the development of the Schiemann reaction in 1927.

⁶² Bancroft and Whearty, *Proc. Natl. Acad. Sci. U.S.A.*, **17**, 153 (1931).

⁶³ Bigelow and Pearson, *J. Am. Chem. Soc.*, **56**, 2773 (1934).

⁶⁴ Bigelow, Pearson, Cook, and Miller, *J. Am. Chem. Soc.*, **55**, 4614 (1933).

⁶⁵ Bockemüller, *Ann.*, **505**, 20 (1933).

⁶⁶ Fredenhagen and Cadenbach, *Ber.*, **67**, 925 (1934).

⁶⁷ Fukuhashi and Bigelow, *J. Am. Chem. Soc.*, **60**, 427 (1938).

⁶⁸ Fukuhashi and Bigelow, *J. Am. Chem. Soc.*, **63**, 2792 (1941).

⁶⁹ Whearty, *J. Phys. Chem.*, **35**, 3121 (1931).

⁷⁰ Calcott, U. S. pat. 2,227,635 [*C.A.*, **25**, 2735 (1941)].

⁷¹ Calcott and Benning, U. S. pat. 2,913,030 [*C.A.*, **29**, 6900 (1935)].

⁷² Daudt and Parmelee, U. S. pat. 2,913,035 [*C.A.*, **29**, 6900 (1935)].

⁷³ E. I. du Pont de Nemours and Co., Fr. pat. 761,945 [*C.A.*, **23**, 4430 (1934)].

⁷⁴ E. I. du Pont de Nemours and Co., Ger. pat. 671,057 [*C.A.*, **33**, 3395 (1933)].

⁷⁵ Fichter, *J. Soc. Chem. Ind.*, **45**, 354 (1922).

⁷⁶ Holleman and Beckman, *Rec. trav. chim.*, **23**, 225 (1904).

⁷⁷ Holleman and Strohower, *Verhandel. Koninkl. Nederl.-d. Akad. Wetenschap.*, **19**, 497 (1911) [*C.A.*, **5**, 1935 (1911)].

⁷⁸ Oswald and Scherer, Ger. pat. 600,705 [*C.A.*, **25**, 7270 (1934)].

⁷⁹ Swarts, *Bull. acad. roy. Belg.*, **1913**, 241 [*C.A.*, **8**, 650 (1914)].

⁸⁰ Schmitt and von Gehren, *J. prakt. Chem.*, [2] **1**, 394 (1870).

⁸¹ Paterno, *Gazz. chim. Ital.*, **11**, 90 (1881).

⁸² Stanley, McMahon, and Adams, *J. Am. Chem. Soc.*, **55**, 705 (1933).

⁸³ Wallach, *Ann.*, **235**, 255 (1885).

⁸⁴ Wallach and Henkel, *Ann.*, **243**, 219 (1885).

Lange and Müller⁴⁵ report the preparation of 4,4'-difluorobiphenyl in low yield by heating the aryl-bis-diazonium fluophosphate, and Wiley⁴⁶ has prepared *p*-fluorobenzoic acid in low yield by the pyrolysis of *p*-carbethoxybenzenediazonium fluosilicate.

A few miscellaneous fluorinating agents such as lead tetrafluoride,⁴⁷ *p*-tolyl iodofluoride,^{48,49} and others have been tried with but slight success.

TABLES OF COMPOUNDS PREPARED BY THE SCHIEMANN REACTION

The compounds which have been prepared by means of the Schiemann reaction are listed in five tables under the following headings:

- I. Benzene Derivatives.
- II. Naphthalene Derivatives.
- III. Biphenyl and Other Polynuclear Hydrocarbon Derivatives.
- IV. Heterocyclic Derivatives.
- V. Compounds with Two Fluorine Atoms Simultaneously Introduced.

Within each table the compounds are listed according to the groups they contain in the following sequence:

| | |
|------------------------|-------------------------------------|
| Fluorine only | Acids |
| Other halogens | Esters |
| Trifluoromethyl groups | Amines, anilides, and azo compounds |
| Alkyl groups | Ketones |
| Phenols | Tetravalent sulfur compounds |
| Ethers | Nitro groups |

The "principle of latest position" has been utilized; a molecule containing more than one of the above groups will be listed with the group which is lowest on the list. For example, 2-fluoro-4-nitrotoluene will be found among the nitro compounds, and 2-fluoro-4-bromoanisole is listed with the ethers.

Included are formulas of several fluoro compounds that have not been prepared by this method. They are present either because their preparation was unsuccessfully attempted or because the intermediate diazonium fluoborate was prepared and used for some reaction other than the Schiemann reaction.

⁴⁵ Lange and Müller, *Ber.*, **63**, 1058 (1930).

⁴⁶ Wiley, U. S. pat. 2,423,359 [*Ch.*, **41**, 6284 (1947)].

⁴⁷ Dimroth and Bockemüller, *Ber.*, **64**, 516 (1931).

⁴⁸ Bockemüller, *Ber.*, **64**, 522 (1931).


⁴⁹ Garvey, Hadley, and Allen, *J. Am. Chem. Soc.*, **55**, 1827 (1933).

There are two columns of references, one for the preparation of the diazonium fluoborates and the other for the preparation of the fluorine compounds from the diazonium fluoborates. This arrangement has been adopted because, as explained above, a diazonium fluoborate has sometimes been prepared but not used in the Schiemann reaction, and also because the best yield in the preparation of a certain diazonium fluoborate is sometimes reported in one paper and the best yield of fluoride obtained by the decomposition of the same fluoborate is reported in another paper.

The entire range of yields reported for each compound is given in the tables. Thus 56-78% means that 56% and 78% are the lowest and highest yields reported. No more than four references for any one compound have been given; if there were more than four references, the four giving the best yields are reported.

The literature has been covered through *Chemical Abstracts* for 1946, although some 1947 articles are included.

TABLE I
BENZENE DERIVATIVES

| Compound | Diazonium Fluoroborate | | | | RN ₂ BF ₄ → RF | |
|--|---|-------------------------------|---------|----------------|--------------------------------------|---------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| <i>Compounds Containing Fluorine Only</i> | | | | | | |
| Fluorobenzene | | 100, 121 | 58-67 | 43, 33, 44, 90 | 51-100 | 1, 33, 89, 44 |
| <i>o</i> -Difluorobenzene | 2-F | 159 | 45 | 23, 38 | 30 | 23, 38 |
| <i>m</i> -Difluorobenzene | † | | | | † | |
| <i>p</i> -Difluorobenzene | 4-F | 154.5 | 64 | 38 | 63 † | 38, 91 |
| 1,2,4-Trifluorobenzene | 2-F, 4-F | 145 | 43 | 27 | 17 | 27 |
| 1,3,4-Trifluorobenzene | 2-F, 5-F | 150 | 59 | 27 | 55, 89 ‡ | 27, 91 |
| 1,2,4,5-Tetrafluorobenzene | 2-F, 4-F, 5-F | — | — | 91 | — | 91 |
| <i>Compounds Containing Other Halogens</i> | | | | | | |
| <i>o</i> -Bromodifluorobenzene | 2-Br | 136 | 30 | 23 | 31, 97 § | 23, 93 |
| <i>m</i> -Bromodifluorobenzene | 3-Br | 141, 143 | 16-45 | 6, 19 | 78, 80 § | 29, 93 |
| <i>p</i> -Bromodifluorobenzene | 4-Br | 133 | 84 | 92, 93 | 75, 82 § | 32, 93 |
| 1,3-Dibromodifluorobenzene | 3-Br, 5-Br | 120 | 72 | 53 | 55 | 53 |
| <i>o</i> -Chlorodifluorobenzene | 2-Cl | 171 | 90-98 | 13, 23, 90 | 65 | 23 |
| <i>m</i> -Chlorodifluorobenzene | 3-Cl | 140, 137 | 91-97 | 7, 45, 90 | 68, 60 § | 46, 94 |
| <i>p</i> -Chlorodifluorobenzene | 4-Cl | — | 90 | 2, 13, 65 | — | 65 |
| 1,4-Dichlorodifluorobenzene | 3-Cl, 4-Cl | — | — | 96 | — | 96 |
| 1,3-Dichlorodifluorobenzene | 3-Cl, 5-Cl | 170-80 | 77 | 97 | 43 | 97 |
| 1,2,4-Trichlorodifluorobenzene | 2-Cl, 4-Cl, 5-Cl | 137 | 73 | 94 | 90 | 94 |
| <i>o</i> -Iododifluorobenzene | 2-I | 89, 100 | 75-80 | 23, 27 | 44-70 | 23, 27 |
| <i>m</i> -Iododifluorobenzene | 3-I | 104, 134 | 81-95 | 6, 27 | 69 | 27 |
| <i>Compounds Containing Trifluoromethyl Groups</i> | | | | | | |
| <i>m</i> -Fluorotrifluoromethylbenzene | 3-CF ₃ | 140 | 79-87 | 50, 83 | 82-92 | 50, 88 |
| 2,5-Difluorotrifluoromethylbenzene | 2-CF ₃ , 4-F | — | 85 | 31 | 67 | 51 |
| 3,5-Difluorotrifluoromethylbenzene | 3-CF ₃ , 5-F | — | 94 | 62 | — | 51 |
| 2,3,5-Trifluorotrifluoromethylbenzene | 2-F, 3-CF ₃ , 5-F | — | — | 99 | — | 99 |
| 2-Fluoro-5-bromotrifluoromethylbenzene | 2-CF ₃ , 4-Br | — | 79 | 100 | 84 | 100 |

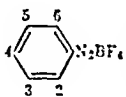
* References 90-142 are on p. 213.

† See Table V.

‡ 58% from *p*-nitroaniline.

§ Over-all yield from air

TABLE I—Continued
 BENZENE DERIVATIVES

| Compound | Diazonium Fluoborate | | | | RN ₂ BF ₄ → RF | |
|----------|---|-------------------------------|---------|-------------|--------------------------------------|-------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |

Compounds Containing Alkyl Groups

| | | | | | | |
|---|--|-----|-------|------------------|--------------|----------|
| <i>o</i> -Fluorotoluene | 2-CH ₃ | 105 | 59-90 | 13, 35, 101, 102 | 90 | 101, 102 |
| <i>m</i> -Fluorotoluene | 3-CH ₃ | 103 | 72-90 | 13, 101, 103 | 87, 87 † | 101, 103 |
| <i>p</i> -Fluorotoluene | 4-CH ₃ | 110 | 67-90 | 1, 13, 60 | 97, 70 † | 1, 14 |
| 2,5-Difluorotoluene | 2-CH ₃ , 4-F | 114 | 62 | 101 | 80 | 101 |
| 2,6-Difluorotoluene | 2-CH ₃ , 3-F | — | — | 45 | 50 † ‡ | 45 |
| 2,4-Dimethylfluorobenzene | 2-CH ₃ , 4-CH ₃ | 105 | 31-47 | 1, 103 | 66-100 | 1, 103 |
| 3,5-Dimethylfluorobenzene | 3-CH ₃ , 5-CH ₃ | 85 | 53 | 104 | 55 ‡ | 104 |
| 1,3-Difluoro-4,6-dimethylbenzene | † ‡ | — | — | — | † ‡ | — |
| 2,4,6-Trimethylfluorobenzene | 2-CH ₃ , 4-CH ₃ , 6-CH ₃ | — | — | 105 | — | 105 |
| Difluoromesitylene | 2-CH ₃ , 4-CH ₃ , 6-CH ₃ , 3-F | — | — | 47 | 83 ‡ | 47 |
| Trifluoromesitylene | 2-CH ₃ , 4-CH ₃ , 6-CH ₃ , 3-F, 5-F | — | — | 47 | 25 ** | 47 |
| 2,6-Dimethyl-4- <i>tert</i> -butylfluorobenzene | 2-CH ₃ , 4- <i>t</i> -C ₄ H ₉ , 6-CH ₃ | — | — | 103 | 70 ‡ | 103 |
| 2,4-Dimethyl-6-bromofluorobenzene | 2-CH ₃ , 4-CH ₃ , 6-Br | 161 | 60 | 105 | Quantitative | 105 |
| 2-Chloro-4-fluorotoluene | 3-Cl, 4-CH ₃ | 125 | — | 107 | 71 ‡ | 107 |
| 2-Chloro-6-fluorotoluene | 2-CH ₃ , 3-Cl | 141 | 80-91 | 45, 103 | 58-81 | 45, 103 |
| 3-Iodo-4-fluorotoluene | 2-I, 4-CH ₃ | 110 | 70 | 109 | 70 | 109 |
| 1,3-Difluoro-2-iodo-4-chloro-6-methylbenzene | 2-I, 3-F, 4-CH ₃ , 6-Cl | 215 | 65 | 54 | 85 | 54 |
| 1,3-Difluoro-2-iodo-4,6-dimethylbenzene | 2-I, 3-F, 4-CH ₃ , 6-CH ₃ | 235 | 65 | 54 | 75 | 54 |

Phenols and Ethers

| | | | | | | |
|-------------------------|-------------------------|-----|----------|-------------|-------------|-------------|
| <i>o</i> -Fluorophenol | 2-OH | — | — | 22 | †† | 22 |
| <i>m</i> -Fluorophenol | 3-OH | — | — | 22 | 50 ‡ | 22 |
| <i>p</i> -Fluorophenol | 4-OH | — | — | 22 | †† | 22 |
| <i>o</i> -Fluoroanisole | 2-OCH ₃ | 125 | 52-91 | 22, 43, 111 | 54-67, 64 ‡ | 29, 43, 110 |
| <i>m</i> -Fluoroanisole | 3-OCH ₃ | 63 | 76-82 ‡† | 23, 29, 30 | 42-64 | 23, 29 |
| <i>p</i> -Fluoroanisole | 4-OCH ₃ | 139 | 85 | 22, 29 | 67, 47 ‡ | 22, 29 |
| 2,4-Difluoroanisole | 3-F, 4-OCH ₃ | 93 | 60 | 110 | 81 | 110 |

* References 90-142 are on p. 228.

† See Table V.

‡ Over-all yield from amine.

†† Preparation not attempted.

‡ Over-all from fluoromesidine.


** Over-all yield from mesitylene

†† Preparation attempted and failed.

‡‡ This diazonium fluoborate, because of its low decomposition point, is likely to decompose spontaneously.

TABLE I—Continued

BENZENE DERIVATIVES

| Compound | Diazonium Fluoroborate | | | | RN ₂ BF ₄ → RF | |
|--------------------------------------|---|-------------------------------|--------------|-------------|--------------------------------------|-------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| 2,6-Difluoroanisole | 2—OCH ₃ , 3—F | — | 85 | 48 | 86 | 48 |
| 3,4-Dimethoxyfluorobenzene | 3—OCH ₃ , 4—OCH ₃ | 123 | 76 | 112 | 1 | — |
| 2-Fluoro-4-bromoisole | 2—OCH ₃ , 5—Br | 156 | 92 | 113 | 84 | 113 |
| 2-Fluoro-4-methylanisole | 2—OCH ₃ , 5—CH ₃ | 150 | 82 | 29 | 45 | 79 |
| 2-Fluoro-6-methylanisole | 2—OCH ₃ , 3—CH ₃ | 88 | 68 | 114 | 62 | 114 |
| 2,6-Difluoro-4-methylanisole | † | — | — | — | † | — |
| 2-Bromo-3-fluoro-4,6-dimethylanisole | 2—Br, 3—OCH ₃ , 4—CH ₃ , 6—CH ₃ | 105 | 70 | 28 | 52.5 | 28 |
| <i>o</i> -Fluorophenetole | 1—OC ₂ H ₅ | 105, 135 | 65-69 | 29, 110 | 33-38 | 29, 110 |
| <i>m</i> -Fluorophenetole | 3—OC ₂ H ₅ | 70 | 75.11 | 29 | 47 | 29 |
| <i>p</i> -Fluorophenetole | 4—OC ₂ H ₅ | 105 | 65-67 | 13, 29, 90 | 33-33 | 29, 42 |
| 2,4-Difluorophenetole | 3—F, 4—OC ₂ H ₅ | 82 | 17-37 | 110, 115 | 0-44 | 110, 115 |
| 4-Fluorodiphenyl ether | 4—OC ₆ H ₅ | 81-3 | 82 | 116 | 67 | 116 |
| 4,4'-Difluorodiphenyl ether | † | — | — | — | † | — |
| 3-Fluoro-4-methoxydiphenyl ether | 2—OCH ₃ , 5—OC ₆ H ₅ | 145 | Quantitative | 114 | Slight | 114 |

Acids and Esters

| | | | | | | |
|---------------------------------------|---|----------|-------|-----------------|-------|---------|
| <i>o</i> -Fluorobenzoic acid | 2—CO ₂ H | 125 | 0-48 | 13, 15, 34, 102 | 10 | 34 |
| <i>m</i> -Fluorobenzoic acid | 3—CO ₂ H | 155 | 34 | 34 | 16 | 34 |
| <i>p</i> -Fluorobenzoic acid | 4—CO ₂ H | — | 75-84 | 13, 15 | 11 | 34 |
| 3,4-Difluorobenzoic acid | 2—F, 5—CO ₂ H | 153 | 77 | 14 | 1 | — |
| 2-Iodo-3-fluorobenzoic acid | 7—I, 3—CO ₂ H | — | — | 82 | 17 | 82 |
| 2-Hydroxy-3-fluorobenzoic acid | 3—CO ₂ H, 4—OH | — | 75-85 | 15 | 1 | — |
| <i>p</i> -Fluorophenylacetic acid | 4—CH ₂ CO ₂ H | — | Free | 34 | 11 | 34 |
| Methyl <i>o</i> -fluorobenzoate | 2—CO ₂ CH ₃ | 102 | 66 | 117 | 83 | 117 |
| Ethyl <i>o</i> -fluorobenzoate | 2—CO ₂ C ₂ H ₅ | 105, 118 | 56-90 | 23, 27 | 90-87 | 23, 27 |
| Ethyl <i>p</i> -fluorobenzoate | 4—CO ₂ C ₂ H ₅ | 93 | 75-94 | 13, 60, 90 | 90 | 60 |
| Methyl 3-fluoro-4-methoxybenzoate | 2—OCH ₃ , 5—CO ₂ CH ₃ | — | 53 | 45 | 84 | 45 |
| Methyl 3,5-difluoro-4-methoxybenzoate | 2—OCH ₃ , 3—F, 5—CO ₂ CH ₃ | — | 82 | 45, 111 | 78-35 | 45, 111 |
| Diethyl 4-fluorophthalate | 5—CO ₂ C ₂ H ₅ , 4—CO ₂ C ₂ H ₅ | 123 | 53 | 118 | 50 | 118 |
| Ethyl <i>p</i> -fluorophenylacetate | 4—CH ₂ CO ₂ C ₂ H ₅ | — | Free | 24 | 11 | 34 |

* References 90-142 are on p. 228.

† See Table V.

‡ Over-all yield from aniline

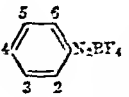
§ Preparation not attempted.

|| Preparation attempted and failed.

‡‡ This diazonium fluoroborate, because of its low decomposition point, is likely to decompose spontaneously.

TABLE I—Continued

BENZENE DERIVATIVES

| Compound | Diazonium Fluoroborate | | | | RN ₂ BF ₄ → RF | |
|---|---|-------------------------------|---------|----------------|--------------------------------------|-----------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| <i>Amines, Amides, and Am Compounds</i> | | | | | | |
| <i>p</i> -Fluorodimethylaniline | 4-N(CH ₃) ₂ | 151 | 55-61 | 119, 120 | 17 | 119 |
| <i>p</i> -Fluoroethylaniline | 4-N(C ₂ H ₅) ₂ | 113 | 83 | 119, 120 | 20 | 119 |
| <i>p</i> -Fluoroacetanilide | 4-NECOCH ₃ | 125 | 84 | 7 | — | 50 |
| <i>p</i> -Fluorophenyl diphenylamine | 4-N(C ₆ H ₅) ₂ | 162 | — | 120 | 1 | — |
| 4-Fluorazobenzene | 4-N=N-C ₆ H ₅ | 145 | 92 | 90, 116 | 16½ | 116 |
| <i>Esters</i> | | | | | | |
| <i>m</i> -Fluoromethylphenone | 3-COCH ₃ | 83 | — | 121 | — | 121 |
| <i>p</i> -Fluoromethylphenone | 4-COCH ₃ | — | 90 | 13 | 1 | — |
| <i>o</i> -Fluoropropiophenone | 2-COC ₂ H ₅ | 81-2 | 72 | 56 | 47½ | 56 |
| <i>m</i> -Fluoropropiophenone | 3-COC ₂ H ₅ | 97-8 | 53 | 56 | 53½ | 56 |
| 4-Fluorobenzophenone | 4-COC ₂ H ₅ | 115 | 90 | 115 | 49½ | 115 |
| 4,4'-Difluorobenzophenone | † | — | — | — | — | — |
| <i>Tetraivalent Sulfur Compounds</i> | | | | | | |
| 4-Fluorobenzenesulfonic acid | 4-SO ₃ H | — | 10 | 15 | 1 | — |
| 3-Fluoro-4-hydroxybenzenesulfonic acid | 2-OH, 5-SO ₃ H | Soluble | — | 15 | 1 | — |
| 4-Fluorobenzenesulfonamide | 4-SO ₂ NE ₂ | — | — | 17 | 1 | — |
| 4,4'-Difluorodiphenylsulfone | †, †† | — | — | — | †, †† | — |
| <i>Nitro Compounds</i> | | | | | | |
| <i>o</i> -Nitrofluorobenzene | 2-NO ₂ | 125 | 53-92 | 8, 12, 14, 22 | 10-19 | 1, 14, 22, 58 |
| <i>m</i> -Nitrofluorobenzene | 3-NO ₂ | 170, 178 | 78-99 | 13, 14, 22, 90 | 43-54 | 14, 22, 23, 58 |
| <i>p</i> -Nitrofluorobenzene | 4-NO ₂ | 156 | 80-100 | 1, 8, 14, 123 | 40-53 | 22, 28, 91, 122 |
| 3,4-Dinitrofluorobenzene | 3-NO ₂ , 4-NO ₂ | 151 | 69 | 53 | 30-39½ | 53 |
| 2,5-Dinitrofluorobenzene | 3-NO ₂ , 5-NO ₂ | 233 | 57 | 124, 125 | 15 | 124, 125 |

* References 90-142 are on p. 228.

† See Table V.



‡ Overall yield from amine.

§ Preparation not attempted.

†† Preparation attempted and failed.

TABLE I—Continued

BENZENE DERIVATIVES

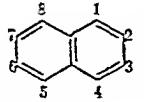
| Compound | Diazonium Fluoroborate | | | | RN ₂ BF ₄ → RF | |
|---|---|-------------------------------|--------------|-------------|--------------------------------------|-------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| 3-Nitro-4-bromofluorobenzene | 3-NO ₂ , 4-Br | 200 | — | 49 | 30 † | 49 |
| 3-Nitro-5-chlorofluorobenzene | 3-NO ₂ , 5-Cl | 190-5 | 76 | 97 | — | 97 |
| 3-Trifluoromethyl-4-nitrofluorobenzene | 3-CF ₃ , 4-NO ₂ | — | 94 | 51 | 41 | 51 |
| 3-Trifluoromethyl-5-nitrofluorobenzene | 3-CF ₃ , 5-NO ₂ | — | 85 | 51 | 49 | 51 |
| 2-Methyl-3-nitrofluorobenzene | 2-CH ₃ , 3-NO ₂ | 116 | 80 | 46 | 63 | 46 |
| 4-Methyl-4-nitrofluorobenzene | 2-CH ₃ , 4-NO ₂ | — | — | 11 | 60 ‡ | 11 |
| 2-Methyl-6-nitrofluorobenzene | 2-CH ₃ , 6-NO ₂ | 143 | 50 | 36 | 20-23 | 86 |
| 3-Nitro-2,4,6-trimethylfluorobenzene | 3-NO ₂ , 2-CH ₃ , 4-CH ₃ , 6-CH ₃ | — | — | 47 | 50-60 ‡ | 47 |
| 2,4-Dimethyl-3-nitrofluorobenzene | 2-CH ₃ , 4-CH ₃ , 5-NO ₂ | 130 | 53 | 28 | 53 | 28 |
| 2-Methyl-4-chloro-5-nitrofluorobenzene | 2-CH ₃ , 4-Cl, 5-NO ₂ | 153 | 61 | 54 | 50 | 54 |
| 2-Bromo-3-nitro-4,6-dimethylfluorobenzene | 2-Br, 3-NO ₂ , 4-CH ₃ , 6-CH ₃ | 105 | 47 | 108 | 45 | 106 |
| 2-Fluoro-4-nitroanisole | 2-OCH ₃ , 5-NO ₂ | 173 | 70-85 | 126, 127 | 10-14 | 126, 127 |
| 3-Fluoro-5-nitroanisole | 3-OCH ₃ , 5-NO ₂ | 150 | 93 | 128, 129 | 36 | 128 |
| 2,6-Difluoro-4-nitroanisole | 2-OCH ₃ , 3-F, 5-NO ₂ | — | 60 | 111 | 10 † | 111 |
| 2-Fluoro-4-nitrophenetole | 2-OC ₂ H ₅ , 5-NO ₂ | 179 | 90 | 127 | 6 | 127 |
| 3-Fluoro-5-nitrophenetole | 3-OC ₂ H ₅ , 5-NO ₂ | 110 | 64 | 125, 129 | 31 | 125, 129 |
| 4-Fluoro-4'-nitrodiphenyl sulfone | 4-() | 145 | Quantitative | 30 | 63 | 30 |

* References 90-142 are on p. 228.

† See Table V.

‡ Over-all yield from aniline.

TABLE II
NAPHTHALENE DERIVATIVES

| Compound | Diazonium Fluoborate | | | | RN ₂ BF ₄ → RF | |
|-------------------------------------|---|-------------------------------|---------|----------------|--------------------------------------|------------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| 1-Fluoronaphthalene | 1-N ₂ BF ₄ | 113 | 62-91 | 1, 35, 90, 130 | 60-68 | 1, 43, 130 |
| 2-Fluoronaphthalene | 2-N ₂ BF ₄ | 108, 116 | 90-97 | 33, 120, 131 | 60-Quantitative | 33, 43, 130, 131 |
| 1,4-Difluoronaphthalene | 1-N ₂ BF ₄ , 4-F | 163 | 47 | 130 | 37 | 130 |
| 1,5-Difluoronaphthalene | † | | | | † | |
| 1,8-Difluoronaphthalene | †, ‡ | | | | †, ‡ | |
| 1-Bromo-2-fluoronaphthalene | 1-Br, 2-N ₂ BF ₄ | 95 | — | 131 | 23 ‡ | 131 |
| 1-Fluoro-4-bromonaphthalene | 1-N ₂ BF ₄ , 4-Br | 152 | 97 | 130 | 65 | 130 |
| 1-Chloro-2-fluoronaphthalene | 1-Cl, 2-N ₂ BF ₄ † | 165 | 50 | 25; see 24 | 90 | 25 |
| 1-Fluoro-8-chloronaphthalene | 1-N ₂ BF ₄ , 8-Cl | 165 | 50 | 132 | 50 | 132 |
| 1-Fluoro-2-methylnaphthalene | 1-N ₂ BF ₄ , 2-CH ₃ | 150 | — | 24 | — | 24 |
| 1-Benzene-2-fluoronaphthalene | 1-N ₂ C ₆ H ₅ , 2-N ₂ BF ₄ | 158 | 31 | 24 | Slight | 24 |
| 1-Fluoro-4-naphthalenesulfonic acid | 1-N ₂ BF ₄ , 4-SO ₃ H | — | — | 120 | † | 130 |
| 1-Nitro-2-fluoronaphthalene | 1-NO ₂ , 2-N ₂ BF ₄ | — | — | — | † | 24, 25 |
| 1-Nitro-8-fluoronaphthalene | 1-N ₂ BF ₄ , 8-NO ₂ | 124 | — | 24 | † | 24 |

* References 90-142 are on p. 228.

† See Table V.

‡ Preparation not attempted.


§ Over-all yield from amine.

|| From 1-nitro-2-aminonaphthalene; see p. 199.

¶ Preparation attempted and failed.

TABLE III

BIPHENYL AND OTHER POLYNUCLEAR HYDROCARBON DERIVATIVES

| Compound | Diammonium Fluoroborate | | | | RN ₃ BF ₄ → RF | |
|---|--|------------------------------|--------------|---------------|--------------------------------------|---------------|
| |  | Decomposition Temperature °C | Yield % | Reference * | Yield % | Reference * |
| 3-Fluorobiphenyl | 2-N ₃ BF ₄ | 81 | 85 | 133 | 89 | 132, 133 |
| 3-Fluorobiphenyl | 3-N ₃ BF ₄ | 61 | 85 | 133 | 60 † | 133, 134 |
| 4-Fluorobiphenyl | 4-N ₃ BF ₄ | 119 | 85-94 | 13, 90, 133 | 82 † | 82, 133 |
| 2,2'-Difluorobiphenyl | ‡ | | | | ‡ | |
| 3,3'-Difluorobiphenyl | ‡ | | | | ‡ | |
| 4,4'-Difluorobiphenyl | ‡ | | | | ‡ | |
| 2,4,4'-Trifluorobiphenyl ‡ | 2-N ₃ BF ₄ , 4-F, 4'-F | 83 | 83 | 133, 136, 137 | 85 | 135, 136, 137 |
| 3,4,4',5-Tetrafluorobiphenyl ‡ | 2-N ₃ BF ₄ , 4-F, 4'-F, 5-F | 103 | 83 | 133, 137 | 91 | 133, 137 |
| 2,2',4,4',5-Pentafluorobiphenyl | ‡, ¶ | | | | ‡, ¶ | |
| 4-Fluoro-4'-bromobiphenyl | 4-N ₃ BF ₄ , 4'-Br | <100 | Quantitative | 139 | 57 | 138 |
| 2-Fluoro-4,4'-dimethylbiphenyl | 2-N ₃ BF ₄ , 4-CH ₃ , 4'-CH ₃ | <100 | 74 | 139 | 91 | 139 |
| 2,2'-Difluoro-4,4'-dimethylbiphenyl | 2-N ₃ BF ₄ , 2'-F, 4-CH ₃ , 4'-CH ₃ | 100 | 90 | 139 | 83 ‡ | 139 |
| 2,2'-Difluoro-6,6'-dimethylbiphenyl | ‡ | | | | ‡ | |
| 3,3'-Dimethyl-4,4'-difluorobiphenyl | ‡ | | | | ‡ | |
| 3,3'-Dimethyl-4,4',6-trifluorobiphenyl | 2-N ₃ BF ₄ , 4-F, 4'-F, 6-CH ₃ , 6'-CH ₃ | 93 | 53 | 140 | 82 | 140 |
| 2-Nitro-2'-fluorobiphenyl | 2-N ₃ BF ₄ , 2'-NO ₂ | 87 | 83 | 52 | 13 | 82 |
| 4-Nitro-4'-fluorobiphenyl | 4-N ₃ BF ₄ , 4'-NO ₂ | 130 | — | 133 | 18 † | 135 |
| 2-Nitro-4,4'-difluorobiphenyl | ‡ | | | | ‡ | |
| 2-Nitro-3'-bromo-4,4'-difluorobiphenyl | ‡ ** | | | | ‡ ** | |
| 2,2'-Dinitro-4,4'-difluorobiphenyl | ‡ | | | | ‡ | |
| 3,3'-Dimethyl-4,4'-difluoro-6-nitrobiphenyl | ‡ | | | | ‡ | |

* References 90-142 are on p. 223.

† Overall yield from aniline.

‡ See Table V.

§ Prepared and erroneously reported as 3,4,4'-trifluorobiphenyl in ref. 135.

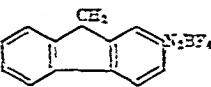
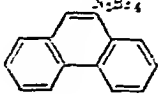
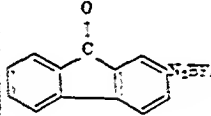
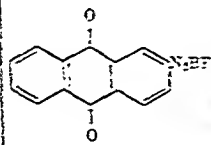
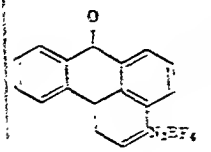
|| Prepared and erroneously reported as 3,4,4',5-tetrafluorobiphenyl in ref. 133.

¶ Preparation attempted and failed.

** Preparation not attempted.

TABLE III—*Continued*

BIPHENYL AND OTHER POLYNUCLEAR HYDROCARBON DERIVATIVES


| Compound | Dioxonium Fluoroborate | | | | BN ₂ BF ₄ → BF | |
|--|---|-------------------------------|---------|-------------|--------------------------------------|-------------|
| | Formula | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| <i>Miscellaneous Polynuclear Hydrocarbon Derivatives</i> | | | | | | |
| 2-Fluorobiphenyl |  | 145 | 75 | 141 | — | 141 |
| 6-Fluorophenanthrene |  | — | — | 53 | 30-42 | 53 |
| 2-Fluorofluorene |  | 150 | — | 141 | 50 † | 141 |
| 2-Fluoranthracene |  | — | 63 | 115 | 60 | 115 |
| 2,11-Fluorobenz[a]anthracene |  | 150 | Quant. | 57 | 50 | 57 |

* References 50-142 are on p. 223.


† Over-all yield from amine.

TABLE IV
 HETEROCYCLIC FLUORINE COMPOUNDS

Pyridine Derivatives

| Compound | Diazonium Fluoborate | | | | RN ₂ BF ₄ → RF | |
|----------------------|---|-------------------------------|---------|-------------|--------------------------------------|-------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| 2-Fluoropyridine | 2-N ₂ BF ₄ | <0 | — | 31 | 34 † | 31 |
| 3-Fluoropyridine | 3-N ₂ BF ₄ | 15 † | — | 31 | 50 † | 31 |
| 4-Fluoropyridine | ‡ | | | 31 | ‡ | 31 |
| 2,6-Difluoropyridine | ‡ ‡ | | | | ‡ ‡ | |

Quandine Derivatives

| Compound | Diazonium Fluoborate | | | | RN ₂ BF ₄ → RF | |
|----------------------------|---|-------------------------------|---------|-------------|--------------------------------------|-------------|
| |  | Decomposition Temperature °C. | Yield % | Reference * | Yield % | Reference * |
| 2-Fluoroquandine | 2-N ₂ BF ₄ | <0 | — | 32 | 25 † | 32 |
| 4-Fluoroquandine | ‡ | 10 | — | 32 | ‡ | 32 |
| 5-Fluoroquandine | 5-N ₂ BF ₄ | 95 | 94 | 32 | 59 † | 32 |
| 6-Fluoroquandine | 6-N ₂ BF ₄ | 90-100 | 96 | 32 | 57 † | 32 |
| 7-Fluoroquandine | 7-N ₂ BF ₄ | 123 | 100 | 32 | 27 † | 32 |
| 8-Fluoroquandine | 8-N ₂ BF ₄ | 133 | 74 | 32 | 24 † | 32 |
| 5-Fluoro-6-methoxyquandine | 5-N ₂ BF ₄ 6-OCH ₃ | — | 83 | 142 | ‡ | 142 |

Quinoxaline Derivatives

| | | | | | | |
|------------------------|--------------------------------------|---|---------------------|----|---|----|
| 6-Fluoro-4-quinoxaline | 4-Quinoxaline-6-diazonium fluoborate | — | Almost quantitative | 12 | ‡ | 12 |
|------------------------|--------------------------------------|---|---------------------|----|---|----|

* References 90-142 are on p. 228.

† Over-all yield from the amine.

‡ This diazonium fluoborate decomposes spontaneously when dry.

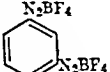
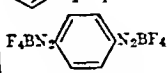
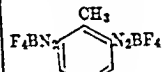
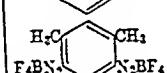
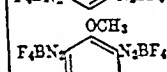
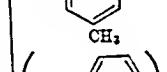
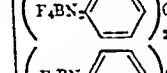
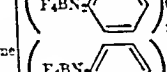
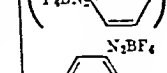
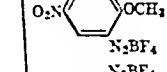
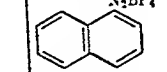
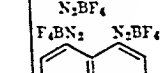
§ Preparation attempted and failed.

|| See Table V.

¶ Preparation not attempted.

TABLE V

COMPOUNDS WITH TWO FLUORINE ATOMS SIMULTANEOUSLY INTRODUCED

| Compound | <i>bis</i> -Diazonium Fluoborate | | | | $R(N_2BF_4)_2 \rightarrow RF_2$ | |
|----------------------------------|---|--------------------------------|--------------|-------------|---------------------------------|-------------|
| | <i>bis</i> -Diazonium Fluoborate | Decomposition Temperature, °C. | Yield % | Reference * | Yield % | Reference * |
| <i>m</i> -Difluorobenzene |  | 206 | 88 | 9, 38 | 31 † | 33 |
| <i>p</i> -Difluorobenzene |  | 186 | 78-82 | 9, 38 | 27 †, ‡ | 33 |
| 2,6-Difluorotoluene |  | — | — | 46 | Slight ‡ | 46 |
| 1,5-Difluoro-2,4-dimethylbenzene |  | — | Quantitative | 9 | ‡ | — |
| 2,6-Difluoro-4-methylanisole |  | — | 43 | 110 | Slight | 110 |
| 4,4'-Difluorodiphenyl ether |  | — | 63 | 116 | 10 † | 116 |
| 4,4'-Difluorobenzophenone |  | 82 | 93 | 116 | 20 † | 116 |
| 4,4'-Difluorodiphenyl sulfone |  | — | — | 30 | ‡ | 30 |
| 2,6-Difluoro-4-nitroanisole |  | — | 52 | 111 | Slight ‡ | 111 |
| 1,5-Difluoronaphthalene |  | 184, 190 | 92 | 120, 131 | 54 | 120, 131 |
| 1,8-Difluoronaphthalene |  | — | 67 | 9 | ‡ | — |
| 2,2'-Difluorodiphenyl |  | 133 | 84 | 140 | 70 | 140 |

* References 90-142 are on p. 228.

† Overall yield from amine.












‡ See Table I.

‡ Preparation not attempted.

‡ Preparation attempted and failed.

TABLE V—Continued

COMPOUNDS WITH TWO FLUORINE ATOMS SIMULTANEOUSLY INTRODUCED

| Compound | bis-Diazonium Fluoroborate | | | | $R(N_2BF_4)_2 \rightarrow RF_2$ | |
|---|---|--------------------------------|---------|-----------------|---------------------------------|-----------------|
| | bis-Diazonium Fluoroborate | Decomposition Temperature, °C. | Yield % | Reference * | Yield % | Reference * |
| 3,3'-Difluorobiphenyl |  | 105 | 98 | 140 | 50 | 140 |
| 4,4'-Difluorobiphenyl |  | 135, 137 | 64-65 | 33, 35, 41, 135 | Low-quantitative 80 † | 33, 41, 49, 136 |
| 2,2',4,4',6-Pentafluorobiphenyl |  | — | ‡ | 140 | ‡ | 140 |
| 2,2'-Difluoro-4,4'-dimethylbiphenyl ** |  | — | — | 139 | — | 139 |
| 3,3'-Difluoro-6,6'-dimethylbiphenyl |  | <100 | 96 | 21 | >17 | 21 |
| 3,3'-Dimethyl-1,4,4'-difluorobiphenyl |  | 123 | — | 135 | 64 † | 135 |
| 2-Nitro-4,4'-difluorobiphenyl |  | 128 | 93 | 135, 137 | 10 | 135, 137 |
| 2-Nitro-3'-bromo-4,4'-difluorobiphenyl |  | — | >79 | 10 | ‡ | — |
| 2,2'-Dinitro-4,4'-difluorobiphenyl |  | <200 | — | 49 | 19 † | 49 |
| 3,3'-Dimethyl-1,4,4'-difluoro-6-nitrophenyl |  | 93 | 95 | 135 | 10 | 135 |
| 2,6-Difluoropyridine |  | — | — | 104 | ‡ | 104 |

* References 90-142 are on p. 228.

† Over-all yield from amine.

‡ Preparation not attempted.

‡ Preparation attempted and failed.

** See Table III.

CHAPTER 5

THE FRIEDEL AND CRAFTS REACTION WITH ALIPHATIC DIBASIC ACID ANHYDRIDES

ERNST BERLINER

Bryn Mawr College

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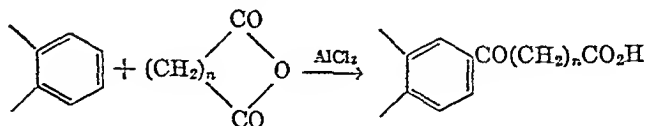
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TABLE

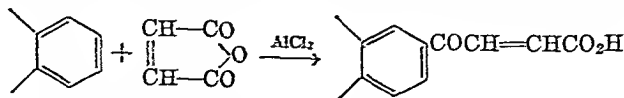
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INTRODUCTION

The Friedel and Crafts reaction between an aliphatic dibasic acid anhydride and an aromatic compound results in the formation of an aroyl fatty acid with the aroyl group situated at the last carbon atom of the aliphatic chain. Since the lowest known dibasic anhydride is succinic anhydride, the number of methylene groups between the carboxyl group



and the carbonyl group cannot be less than two. β -Aroylpropionic acids are therefore the lowest members of the series that can be prepared by the general reaction. Acids such as benzoylformic and benzoylacetic acid are not accessible by this procedure, and their synthesis is beyond the scope of this discussion. When maleic anhydride (or a substituted maleic anhydride) is used instead of the saturated anhydride, a β -benzoylacrylic acid is obtained. Burcker introduced the reaction in

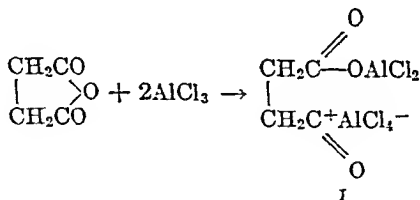


1882, when he condensed succinic anhydride with benzene in the presence

led to the preparation of many new acids, to an improved technique, and to a greater knowledge of the reaction. In this way many new hydrocarbons have been synthesized by Haworth, Fieser, and others, and the structures of many natural products elucidated.^{9,10,11} Since so much more is known at the present time about the reaction with succinic anhydride than with all the other anhydrides, the following discussion is primarily concerned with this reagent; the others will be included in special sections.

MECHANISM

According to the work of Noller and Adams¹² and the investigations of Groggins and Nagel,¹³ the Friedel and Crafts reaction with an anhydride proceeds with a maximum yield when two moles of aluminum chloride are used per mole of anhydride. According to Groggins and Nagel one mole of catalyst brings about the fission of the anhydride with the formation of the aluminum chloride salt of one carboxyl group and the formation of the acid chloride from the second carboxyl group.¹⁴ The second mole of aluminum chloride functions as the catalyst as in a typical Friedel and Crafts acylation. In harmony with these views and the present theories of aromatic substitution the reaction can therefore be visualized as proceeding through the complex I, which attacks the



aromatic ring by virtue of the electrophilic center on the acyl ion. The preferential fission of unsymmetrical anhydrides can be explained if the assumption is made that the electron-seeking aluminum chloride opens the anhydride toward the carboxyl group that has the higher electron density. The effect of substitution is not great with methylsuccinic anhydride but is pronounced with the *para*-substituted phenyl-

⁹ Fieser, *Chemistry of Natural Products Related to Phenanthrene*, 2nd ed., pp. 71-75, Reinhold Publishing Corp., New York, 1937.

¹⁰ Linstead, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **33**, 336 (1936).

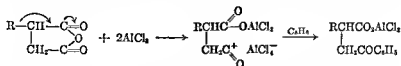
¹¹ Springall, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **35**, 301 (1939).

¹² Noller and Adams, *J. Am. Chem. Soc.*, **45**, 1889 (1924).

¹³ Groggins and Nagel, *Ind. Eng. Chem.*, **25**, 1313 (1934); Groggins, *Unit Processes in Organic Synthesis*, 3rd ed., p. 761-762, McGraw-Hill Book Co., New York, 1947.

¹⁴ Evidence for the formation of such a complex is presented by Saboor, *J. Chem. Soc.*, **1945**, 922.

succinic anhydrides listed on p. 245, which are cleaved in accordance with the character of the substituents. The dual nature of the phenyl group could account for the formation of both acids in equal amounts



when phenylsuccinic anhydride is condensed with benzene.¹⁵ Nitrobenzene, when employed as a solvent, accentuates preferential cleavage in one direction,^{16,17} which may be due to the solvent power of nitrobenzene or to its greater ionizing power.^{14,18} Other mechanisms for the reaction of unsymmetrical anhydrides have been advanced.^{6,14,16,18}

SCOPE AND LIMITATIONS

The reaction between an anhydride and an aromatic compound in the presence of anhydrous aluminum chloride is a Friedel and Crafts reaction; it is therefore applicable to all those aromatic compounds on which that type of reaction can be carried out, i.e., aromatic hydrocarbons, their halogen derivatives, phenols and phenolic ethers, and many heterocyclic compounds. Recently the successful condensation of succinic anhydride and acetanilide has been reported.¹⁹ Compounds having nitro, carboxyl, carbonyl, and similar deactivating groups which impede the Friedel and Crafts reaction cannot be utilized. If the deactivating group is removed from the aromatic ring by a few methylene groups, the reaction becomes possible, as has been shown for ethyl β -phenylpropionate or β -phenylpropionitrile.^{20,21}

The yields in succinoylations are usually fair or good (between 50% and 100%), although some much lower yields have been reported, particularly with substituted succinic anhydrides or with halogenated benzene derivatives, which of all compounds have been studied least. Only a few reactions have failed completely or failed to yield the expected product. Guaiacol and hydroquinone monomethyl ether are reported not

¹⁵ Ali, Desai, Hunter, and Muhammad, *J. Chem. Soc.*, **1937**, 1013.

¹⁶ Desai and Wali, *Proc. Indian Acad. Sci.*, **6A**, 135 (1937) [*C.A.*, **32**, 508 (1938)].

¹⁷ Wali, Khalil, Bhatia, and Ahmad, *Proc. Indian Acad. Sci.*, **14A**, 139 (1941) [*C.A.*, **36**,

1508 (1942)].

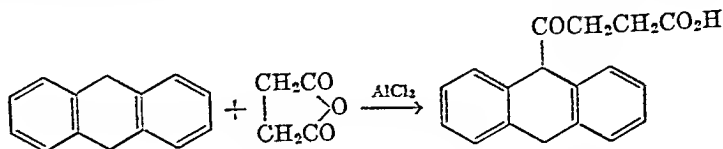
¹⁸ Rothstein and Saboor, *J. Chem. Soc.*, **1943**, 425.

¹⁹ English, Clapp, Cole, and Krapcho, *J. Am. Chem. Soc.*, **67**, 2263 (1945).

²⁰ Borsche and Sinn, *Ann.*, **553**, 260 (1942).

²¹ See also Fieser and Heymann, *J. Am. Chem. Soc.*, **63**, 2333 (1941), for the reaction between phthalic anhydride and γ -phenylbutyric acid.

to react with succinic anhydride under a variety of different conditions in nitrobenzene, tetrachloroethane, or carbon disulfide as the solvent.^{22,*} At elevated temperatures demethylation of phenolic ethers often occurs.^{22,24,25} Pyrogallol trimethyl ether yields β -(2-hydroxy-3,4-dimethoxybenzoyl)propionic acid in all solvents that have been employed;^{22,27,23} when, however, the organic layer is separated from the aqueous acidic layer before steam distillation, a small amount of the undemethylated acid is obtained.^{22a} 9,10-Dihydroanthracene with succinic anhydride and aluminum chloride in nitrobenzene solution undergoes substitution in the aliphatic 9-position²² instead of the 2-



position as expected by analogy with the behavior of tetralin. A small amount of the same acid was also obtained from anthracene directly when benzene was used as solvent.²³ With a large excess of catalyst substitution occurred in the 2-position only.²¹ *p*-Di-*tert*-butylbenzene reacts with succinic anhydride in carbon disulfide with elimination of one *tert*-butyl group; β -(*p*-*tert*-butylbenzoyl)propionic acid is formed together with a small amount of an unidentified acid.²¹

Types of Compounds Condensed with Succinic Anhydride

Hydrocarbons. A great number of methylated benzenes have been successfully condensed with succinic anhydride. Toluene, the three xylenes, mesitylene, the tetramethylbenzenes, and pentamethylbenzene can be converted into the corresponding methylated β -aroylpropionic

* Guaiacol and succinic anhydride have been shown to react in a mixture of tetrachloroethane and nitrobenzene to form β -(4-hydroxy-3-methoxybenzoyl)propionic acid in low yield. Holmes and Trevor, *Can. J. Research*, **22**, 109 (1944).

²² Dalal and Nargund, *J. Indian Chem. Soc.*, **14**, 495 (1937).

^{22a} Perkin and Robinson, *J. Chem. Soc.*, **93**, 459 (1905).

²³ Hill, Short, and Stromberg, *J. Chem. Soc.*, **1937**, 937.

²⁴ Rice, *J. Am. Chem. Soc.*, **50**, 229 (1928).

²⁵ Bargellini and Guaz, *Gazz. chim. Ital.*, **42**, I, 197 (1912).

²⁷ Dalal, Bokil, and Nargund, *J. Univ. Bombay*, **8**, Pt. 3, 203 (1939) [*C.A.*, **34**, 2821 (1940)].

²² Mitter and De, *J. Indian Chem. Soc.*, **16**, 35 (1939).

^{22a} Manske and Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945).

²³ Cook, Robinson, and Roe, *J. Chem. Soc.*, **1939**, 266.

²² Berliner, unpublished results.

²¹ Price, Shafer, Huber, and Bernstein, *J. Org. Chem.*, **7**, 517 (1942).

acids in good yields.^{7,32,33} Alkylated benzene derivatives having alkyl groups larger than methyl that have been employed as starting materials in the reaction include ethylbenzene,^{7,32,34} cumene,^{32,35} *p*-cymene,³² *o*-ethyltoluene,³² *tert*-butylbenzene,³⁵ and *tert*-amylbenzene.³⁶ Migration or isomerization of larger groups, which often accompanies Friedel and Crafts reactions,³⁷ has not been observed in succinoylations; but compounds such as *n*-propyl- or *n*-butylbenzene, with which such isomerizations might be expected to take place, have not been studied extensively. *n*-Propylbenzene has been converted to β -(4-*n*-propylbenzoyl)propionic acid without isomerization of the *n*-propyl group.^{37a}

Naphthalene and its alkyl derivatives have been the most thoroughly studied of all the polynuclear hydrocarbons, and a great number of phenanthrene derivatives have been synthesized through the appropriate β -naphthoylpropionic acid.^{33,38,40} Phenanthrene,^{41,42} anthracene,^{31,39,43,44} pyrene,^{45,46,47} retene,^{48,49} and chrysene^{50,51} condense fairly readily with succinic anhydride, as do also some methyl derivatives of phenanthrene.^{52,53,54} Partially hydrogenated aromatic compounds and

³¹ Muhr, *Ber.*, **23**, 3215 (1895).

³² Barnett and Sanders, *J. Chem. Soc.*, **1933**, 434.

³³ Levy, *Ann. Chim.*, [11] **9**, 5 (1933).

³⁴ Fieser and Price, *J. Am. Chem. Soc.*, **55**, 1833 (1933).

³⁵ (a) Fieser, Berhner, Bondhus, Chang, Dauben, Ltlhinger, Fawas, Fields, Heidelberger, Heymann, Vaughan, Wilson, Wilson, Mao-i Wu, and (b) Leffler, Hamlin, Matson, Moore, Moore, and Zaugg, *J. Am. Chem. Soc.*, **70**, 3174, 3197 (1948).

³⁷ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, p. 94, Reinhold Publishing Corp., New York, 1941. Haworth, Latsky, and Mavin (ref. 112 below) condensed succinic anhydride with the hydrocarbon obtained from naphthalene and *n*-propyl bromide in the presence of aluminum chloride. The resulting keto acid was not identical with β -(6-isopropyl-2-naphthoyl)propionic acid and was probably β -(6-*n*-propyl-2-naphthoyl)propionic acid, i.e., the succinoylation proceeded without isomerization.

^{37a} Smith and Chien-Pen Lo, *J. Am. Chem. Soc.*, **70**, 2309 (1948).

³⁸ Haworth et al., *J. Chem. Soc.*, **1932**, 1125, 1784, 2343, 2720.

³⁹ Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4347 (1932).

⁴⁰ Bachmann and Struve, *J. Org. Chem.*, **4**, 472 (1939).

⁴¹ Haworth and Mavin, *J. Chem. Soc.*, **1933**, 1012.

⁴² Bachmann and Bradbury, *J. Org. Chem.*, **2**, 175 (1937-1938).

⁴³ Cook and Robinson, *J. Chem. Soc.*, **1938**, 505.

⁴⁴ Bergmann and Weigmann, *J. Chem. Soc.*, **1938**, 1243.

⁴⁵ Cook, Hewett, and Hieger, *J. Chem. Soc.*, **1933**, 395.

⁴⁶ Fieser and Fieser, *J. Am. Chem. Soc.*, **57**, 732 (1935).

⁴⁷ Winterstein, Vetter, and Schön, *Ber.*, **68**, 1079 (1935).

⁴⁸ Adelson and Bogert, *J. Am. Chem. Soc.*, **59**, 1776 (1937); Cassaday and Bogert, *ibid.* **63**, 703 (1941).

⁴⁹ Fieser and Clapp, *J. Am. Chem. Soc.*, **63**, 319 (1941).

⁵⁰ Beyer, *Ber.*, **71**, 915 (1938).

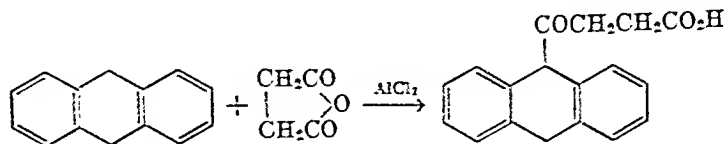
⁵¹ Cook and Graham, *J. Chem. Soc.*, **1944**, 329.

⁵² Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2350 (1940).

⁵³ Bachmann and Cortes, *J. Am. Chem. Soc.*, **65**, 1329 (1943).

⁵⁴ Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 1293 (1940).

to react with succinic anhydride under a variety of different conditions in nitrobenzene, tetrachloroethane, or carbon disulfide as the solvent.^{22*} At elevated temperatures demethylation of phenolic ethers often occurs.^{23,24,25} Pyrogallol trimethyl ether yields β -(2-hydroxy-3,4-dimethoxybenzoyl)propionic acid in all solvents that have been employed;^{26,27,28} when, however, the organic layer is separated from the aqueous acidic layer before steam distillation, a small amount of the undemethylated acid is obtained.^{28a} 9,10-Dihydroanthracene with succinic anhydride and aluminum chloride in nitrobenzene solution undergoes substitution in the aliphatic 9-position²⁹ instead of the 2-



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²² Delal and Nargund, *J. Indian Chem. Soc.*, **14**, 496 (1937).

²³ Perkin and Robinson, *J. Chem. Soc.*, **93**, 459 (1905).

²⁴ Hill, Short, and Stromberg, *J. Chem. Soc.*, 1937, 937.

²⁵ Rice, *J. Am. Chem. Soc.*, **50**, 229 (1928).

²⁶ Bargezzini and Gina, *Gazz. chim. Ital.*, **42**, I, 197 (1912).

²⁷ Delal, Bohil, and Nargund, *J. Univ. Bombay*, **8**, Pt. 3, 203 (1939) [*C.A.*, **34**, 2821 (1940)].

²⁸ Mitter and De, *J. Indian Chem. Soc.*, **16**, 35 (1939).

^{28a} Manabe and Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945).

²⁹ Cook, Robinson, and Roe, *J. Chem. Soc.*, 1939, 266.

³⁰ Berliner, unpublished results.

³¹ Price, Shafer, Huber, and Bernstein, *J. Org. Chem.*, **7**, 517 (1942).

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³² Muhr, *Ber.*, **23**, 3215 (1895).

³³ Barnett and Sanders, *J. Chem. Soc.*, **1933**, 434.

³⁴ Levy, *Ann. chim.*, [11] **9**, 5 (1938).

³⁵ Fieser and Price, *J. Am. Chem. Soc.*, **58**, 1838 (1936).

³⁶ (a) Fieser, Berliner, Bondhus, Chang, Dauben, Ettlinger, Fawcett, Fields, Haidelberger, Heymann, Vaughan, Wilson, Wilson, Mao-i Wu, and (b) Leffer, Hamlin, Matson, Moore, Moore, and Zaugg, *J. Am. Chem. Soc.*, **70**, 3174, 3197 (1948).

³⁷ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, p. 94, Reinhold Publishing Corp., New York, 1941. Haworth, Letsky, and Mavin (ref. 112 below) condensed succinic anhydride with the hydrocarbon obtained from naphthalene and *n*-propyl bromide in the presence of aluminum chloride. The resulting keto acid was not identical with β -(6-isopropyl-2-naphthoyl)propionic acid and was probably β -(6-*n*-propyl-2-naphthoyl)propionic acid; i.e., the succinoylation proceeded without isomerization.

^{37a} Smith and Chien-Pen Lo, *J. Am. Chem. Soc.*, **70**, 2209 (1948).

³⁸ Haworth et al., *J. Chem. Soc.*, **1932**, 1125, 1784, 2243, 2720.

³⁹ Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4347 (1932).

⁴⁰ Bachmann and Struve, *J. Org. Chem.*, **4**, 472 (1939).

⁴¹ Haworth and Mavin, *J. Chem. Soc.*, **1933**, 1012.

⁴² Bachmann and Bradbury, *J. Org. Chem.*, **2**, 175 (1937-1938).

⁴³ Cook and Robinson, *J. Chem. Soc.*, **1938**, 505.

⁴⁴ Bergmann and Weismann, *J. Chem. Soc.*, **1938**, 1243.

⁴⁵ Cook, Hewett, and Hieger, *J. Chem. Soc.*, **1933**, 395.

⁴⁶ Fieser and Fieser, *J. Am. Chem. Soc.*, **67**, 782 (1935).

⁴⁷ Winterstein, Vetter, and Schön, *Ber.*, **63**, 1079 (1935).

⁴⁸ Adelson and Bogert, *J. Am. Chem. Soc.*, **59**, 1776 (1937); Casaday and Bogert, *ibid.*, **63**, 703 (1941).

⁴⁹ Fieser and Clapp, *J. Am. Chem. Soc.*, **63**, 319 (1941).

⁵⁰ Beyer, *Ber.*, **71**, 915 (1938).

⁵¹ Cook and Graham, *J. Chem. Soc.*, **1944**, 329.

⁵² Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2550 (1940).

⁵³ Bachmann and Cortes, *J. Am. Chem. Soc.*, **65**, 1329 (1943).

⁵⁴ Fieser and Cason, *J. Am. Chem. Soc.*, **62**, 1293 (1940).

compounds having aliphatic rings that have been employed in succinoylations include hydrindene,^{55,56,57} fluorene,⁵⁸ acenaphthene,⁵⁹ tetralin,^{7,59} as well as partially hydrogenated anthracene,^{21,29} phenanthrene,⁶⁰ retene,⁴⁹ pyrene,⁴⁵ and acephenanthrene.⁶¹ Reaction with these compounds often proceeds with higher yields than with the fully aromatic compounds and leads to a single product (compare p. 239). Among the bicyclic compounds that have been employed are biphenyl,^{62,63} diphenylmethane,^{23,26} and phenylcyclohexane.^{26,61} All four halogenated benzenes^{26,65,66,67} and *o*-chlorotoluene²⁶ have been converted into the corresponding *p*-halobenzoylpropionic acids, but no halogen derivatives of polynuclear hydrocarbons or of compounds having more than one halogen atom have been tried.⁶³

Phenolic Ethers and Free Phenols. Phenolic ethers, which undergo the succinoylation reaction particularly readily, have been extensively studied. The compounds utilized include anisole,^{24,62,70,71} many ethers of phenol with alkyl groups larger than methyl,^{2,72,73} all three cresol methyl ethers,^{74,75} and a number of derivatives of anisole with more and larger alkyl groups,⁷⁶⁻⁷⁹ as well as *o*-chloroanisole and *o*-chlorophenetole.⁸⁰ The α - and β -methoxynaphthalenes have been readily converted into the

⁵⁵ Fieser and Seligman, *J. Am. Chem. Soc.*, **59**, 883 (1937).

⁵⁶ Sengupta, *J. Indian Chem. Soc.*, **16**, 89 (1939).

⁵⁷ McQuillin and Robinson, *J. Chem. Soc.*, **1941**, 586.

⁵⁸ Koelsch, *J. Am. Chem. Soc.*, **55**, 3885 (1933).

⁵⁹ Newman and Zahn, *J. Am. Chem. Soc.*, **65**, 1007 (1943).

⁶⁰ See p. 240.

⁶¹ Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4373 (1932).

⁶² Weizmann, Bergmann, and Bograchow, *Chemistry & Industry*, **59**, 402 (1940).

⁶³ Hey and Wilkinson, *J. Chem. Soc.*, **1940**, 1030.

⁶⁴ Buu-Hoi, Cagniant, and Metzner, *Bull. soc. chim. France*, **11**, 127 (1944).

⁶⁵ Skraup and Schwamberger, *Ann.*, **462**, 135 (1925).

⁶⁶ Fieser and Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

⁶⁷ Chovin, *Ann. chim.*, [11] **9**, 447 (1935).

⁶⁸ Haworth and Mavin, *J. Chem. Soc.*, **1932**, 2720, reported that the condensation of 4-bromo-1-methylnaphthalene with succinic anhydride seemed unpromising.

⁶⁹ Poppenberg, *Ber.*, **34**, 3257 (1901).

⁷⁰ Hahn, *J. Am. Chem. Soc.*, **38**, 1517 (1916).

⁷¹ Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2314 (1936).

⁷² Rice, *J. Am. Chem. Soc.*, **45**, 2319 (1924).

⁷³ Trivedi and Nargund, *J. Univ. Bombay*, **11**, Pt. 3, 127 (1942) [*C.A.*, **37**, 2005 (1943)].

⁷⁴ Rosenmund and Schapiro, *Arch. Pharm.*, **272**, 313 (1934) [*C.A.*, **28**, 4046 (1934)].

⁷⁵ Desai and Wali, *Proc. Indian Acad. Sci.*, **6A**, 144 (1937) [*C.A.*, **32**, 509 (1938)].

⁷⁶ Fieser and Lothrop, *J. Am. Chem. Soc.*, **58**, 2050 (1936).

⁷⁷ Harland and Robertson, *J. Chem. Soc.*, **1939**, 937.

⁷⁸ Cocker, *J. Chem. Soc.*, **1945**, 36.

⁷⁹ Soloveva and Preobrazhenskii, *J. Gen. Chem. U.S.S.R.*, **15**, 60 (1945) [*C.A.*, **40**, 1820 (1946)].

⁸⁰ Nguyen-Hoan and Buu-Hoi, *Compt. rend.*, **224**, 1228 (1947).

succinoylated products in good yields,^{22,71,81-84} as have also the dimethyl ethers of the three dihydric phenols,^{22,23,26,28,71} the trimethyl ether of pyrogallol,^{26,27,28} and hydroxyhydroquinone.²⁶ 1,5- and 2,6-Dimethoxynaphthalene react smoothly with succinic anhydride with the formation of the corresponding dimethoxy- β -naphthoylpropionic acids.^{24,67} Free phenols, such as phenol itself,^{22,85,89} the cresols,⁸³ resorcinol,⁸⁰ and orcinol,⁸⁰ are succinoylated only under more drastic conditions at elevated temperatures, and mixtures are often obtained. The failure of guaiacol and the monomethyl ether of hydroquinone to undergo reaction has already been mentioned,²² as has also the partial demethylation of methyl ethers which are sometimes split by aluminum chloride. Diphenyl ether^{24,91,92,93} and diphenyl sulfide^{93a} afford the corresponding acids in almost quantitative yields.

Heterocyclic Compounds. Thiophene,⁹⁴ dimethylthiophene,⁹⁵ benzo-⁹⁶ and dibenzo-thiophene,⁹⁷ and thiochroman⁹⁸ are sulfur-containing heterocyclic compounds that have been condensed with succinic anhydride. Diphenylene oxide^{99,100,101} reacts with succinic anhydride as expected, but carbazole and its N-methyl derivative react with two moles of the anhydride; the mono acid has not been isolated.^{102,103} N-Acetylphenothiazine, however, yields a mono acid on succinoylation.¹⁰⁴

⁸¹ Ruzicka and Waldmann, *Helv. Chim. Acta*, **15**, 907 (1932).

⁸² Bachmann and Holmes, *J. Am. Chem. Soc.*, **62**, 2753 (1940).

⁸³ Bachmann and Morin, *J. Am. Chem. Soc.*, **66**, 553 (1944).

⁸⁴ Hill, Short, and Ilginbottom, *J. Chem. Soc.*, 1936, 317.

⁸⁵ Bachmann and Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).

⁸⁶ Short, Stromberg, and Wiles, *J. Chem. Soc.*, 1936, 319.

⁸⁷ Desai and Wali, *J. Univ. Bombay*, **5**, Pt. 2, 73 (1936) [*C.A.*, **31**, 3033 (1937)].

⁸⁸ Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2382 (1936).

⁸⁹ Raval, Bokil, and Nargund, *J. Univ. Bombay*, **7**, Pt. 3, 184 (1938) [*C.A.*, **33**, 3770 (1939)].

⁹⁰ Fieser, Gates, and Kilmer, *J. Am. Chem. Soc.*, **62**, 2963 (1940).

⁹¹ Desai and Shroff, *J. Univ. Bombay*, **10**, Pt. 3, 97 (1941) [*C.A.*, **35**, 3795 (1942)].

⁹² Kipper, *Ber.*, **33**, 2490 (1905).

⁹³ Rice, *J. Am. Chem. Soc.*, **48**, 269 (1926).

⁹⁴ Huang-Minlon, *J. Am. Chem. Soc.*, **63**, 2487 (1941).

⁹⁵ Fieser, Moser, and Paulshock, unpublished results.

⁹⁶ Fieser and Kenelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

⁹⁷ Steinkopf, Poulsson, and Herdey, *Ann.*, **536**, 123 (1938).

⁹⁸ Buu-Hoi and Cagniant, *Ber.*, **76**, 1269 (1943).

⁹⁹ Gilman and Jacoby, *J. Org. Chem.*, **3**, 103 (1938).

¹⁰⁰ Cagniant and Deluzarche, *Compt. rend.*, **223**, 1012 (1946).

¹⁰¹ Mayer and Krieger, *Ber.*, **55**, 1659 (1922). The authors also mention an acid obtained from succinic anhydride and tetrahydrodiphenylene oxide, but they give no details.

¹⁰² Mosettig and Robinson, *J. Am. Chem. Soc.*, **57**, 902 (1935).

¹⁰³ Gilman, Parker, Bahe, and Brown, *J. Am. Chem. Soc.*, **61**, 2836 (1939).

¹⁰⁴ Mitchell and Plant, *J. Chem. Soc.*, 1936, 1295.

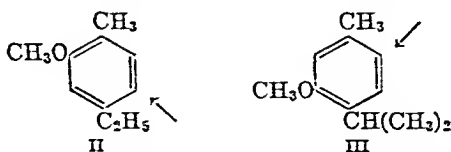
¹⁰⁵ Rejnowski and Suszko, *Arch. Chem. i Farm. Warsaw*, **3**, 135 (1937) (*Chem. Zentr.* 1937, II, 3748).

¹⁰⁶ Baltaly, Harfenist, and Webb, *J. Am. Chem. Soc.*, **63**, 2673 (1941).

Orientation of Entering Groups

The position at which substitution occurs in the aromatic ring is determined by the group already present and can be predicted from the rules governing aromatic substitution. The course of the reaction, however, appears to be subject to some steric hindrance, as is generally true with Friedel and Crafts reactions. Succinic anhydride is relatively large and avoids in most instances the *ortho* position; hence reaction occurs at the *para* position if possible. Otherwise *ortho* substitution occurs without great difficulty. Thus only the *para* isomer is formed in the succinoylation of toluene or ethylbenzene,^{7,22,24} which in other substitution reactions are invariably attacked in both the *ortho* and *para* positions. On the other hand, *p*-xylene and mesitylene are necessarily substituted *ortho* to a methyl group.^{22,23} The halogenated benzenes likewise are only attacked in the *para* positions.^{24,25,26,27} The succinoylation of phenols is exceptional in that *ortho* substitution predominates. Whereas anisole, phenetole,^{2,23-25} and higher alkyl ethers of phenol are substituted exclusively in the position *para* to the alkoxy group, phenol and succinic anhydride furnish a mixture of *ortho* and *para* isomers in which the *ortho* predominates.^{23,25,29}

Two isomeric acids are also formed in the reaction of succinic anhydride with *o*- and *m*-cresol, but *p*-cresol is attacked only in the position *ortho* to the hydroxyl group.⁵³ When the methyl ethers of the cresols are employed as starting materials, the anhydride always attaches itself to the position that corresponds to the stronger directing influences of the methoxyl group.^{74,75} This is also true for higher alkylated derivatives of anisole, such as compounds II and III, which are always substituted *para* to the methoxyl group.^{77,79} *o*-Chlorotoluene is succinoylated in



the *para* position to the chlorine atom.²⁵ Although few disubstituted derivatives of the above type have been investigated, succinoylations may always be expected to follow the course of the Friedel and Crafts acylation, possibly with still more stress on unhindered positions. If additional isomers of the above compounds are formed, the amounts are so small that they have escaped detection.

Diphenyl ether and diphenyl sulfide are succinoylated in almost quantitative yields in the *para* positions,^{24,25,26,27,28} and only the formation

of one isomer is reported in the reactions with biphenyl,^{62,63} diphenylmethane,^{23,36} and phenylcyclohexane.^{36,64} 4-Methoxybiphenyl, however, furnishes both the 4' and the 3 derivatives.¹⁰⁵

In the succinoylation of polynuclear hydrocarbons two isomeric acids are often produced, but separation can usually be effected quite easily. Naphthalene is substituted in both the 1- (36%) and 2- (47%) positions, and the isomers can readily be separated by virtue of the greater solubility of the 1-acid.^{4,39} Anthracene also affords two isomeric acids, but the 1-acid is formed to a much smaller extent.⁴¹ Phenanthrene forms predominantly the 3-acid, with a small amount of the 2-acid.^{41,42} The isolation of the predominant acid from both anthracene and phenanthrene offers no difficulties. The reaction between pyrene and succinic anhydride results in the formation of the 1-acid in almost quantitative yield,^{44,45,47} and chrysene yields predominantly the 2-acid with a small amount of an isomer.^{30,31} Partially hydrogenated aromatic compounds are often employed as starting materials to avoid polysubstitution or to effect substitution in a position different from the one attacked in the parent hydrocarbon. In addition, the yields with these compounds are generally higher than with the fully aromatic compounds. For instance, tetralin is substituted exclusively in the 2-position,^{7,48} whereas naphthalene yields a mixture of the 1- and 2-acids.^{4,38,40} Retene is substituted in position 3 in 58.5% yield; dihydroretene affords the 2-acid in 80% yield.^{44,49} Hydrogenated phenanthrene derivatives have been employed quite extensively, and dehydrogenation to the fully aromatic acids offers no difficulties. The formulas on page 240 illustrate the different points of attack on the hydrogenated phenanthrene nucleus.^{40,41,42,106-111} Pyrene and hexahydropyrene are likewise substituted in two different positions.⁴³ Hydrindene and fluorene yield only one substitution product;⁴²⁻⁴⁵ but two acids are obtained from acenaphthene, predominantly the 3-acid, which can easily be obtained in a very pure state.²⁹

When the naphthalene ring is substituted by an alkyl or a methoxyl group, only one acid is usually isolated. 1-Methyl- and 1-ethyl-naphthalene are substituted exclusively in the 4-position,^{40,43} while 2-methyl-

¹⁰⁶ Fieser and Bradsher, *J. Am. Chem. Soc.*, **55**, 1735 (1936).

¹⁰⁷ 1,2,3,4-Tetrahydrophenanthrene. Bachmann and Struve, *ref. 40*, and Bachmann and Struve, *J. Org. Chem.*, **5**, 416 (1940).

¹⁰⁸ 1,2,3,4,9,10,11,12-Octahydrophenanthrene: Cook and Haslewood, *J. Chem. Soc.*, 1935, 767.

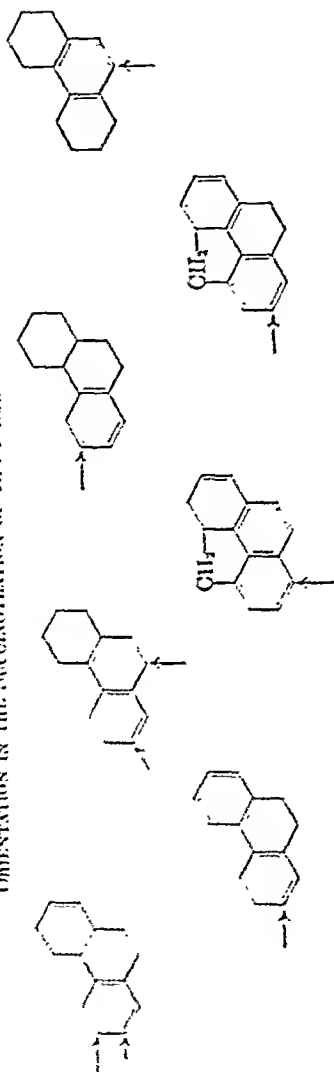
¹⁰⁹ 1,2,3,4,5,6,7,8-Octahydrophenanthrene: van de Kamp, Burger, and Moettig, *J. Am. Chem. Soc.*, **60**, 1321 (1938).

¹¹⁰ 9,10-Dihydrophenanthrene. Burger and Moettig, *J. Am. Chem. Soc.*, **59**, 1302 (1937).

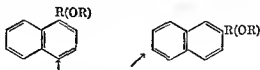
¹¹¹ 9,10-Dihydrophenanthrene. Fieser and Johnson, *J. Am. Chem. Soc.*, **61**, 168, 1647 (1939).

¹¹² 9,10-Dihydro-4,5-methylenepheneanthrene: Fieser and Casco, *J. Am. Chem. Soc.*, **62**, 1203 (1940).

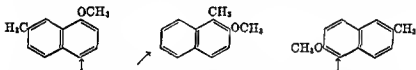
ORIENTATION IN THE SUCCINOYLATION OF THE PHENANTHRENE NUCLEI



naphthalene, and in general 2-alkylnaphthalenes, react predominantly, but not exclusively, in position 6.^{35,39,112,113,114} Only one acid is formed in reactions with succinic anhydride and 2,3-dimethyl-¹¹⁵ and 2,7-dimethyl-naphthalene.³⁹ When methoxyl groups are situated in positions 1 or 2 of the naphthalene ring, the anhydride attaches itself predomi-



nantly to positions 4 or 6 (the latter in nitrobenzene solution) just as it does in the methylnaphthalenes,^{33,71,81,85} and only one isomer is formed from 1,5- and 2,6-dimethoxynaphthalene.^{24,27} The stronger directive influence of the methoxyl group is borne out in the succinoylations of 1-methoxy-7-methyl-,⁸¹ 1-methyl-2-methoxy-,⁸⁴ and 2-methyl-6-methoxynaphthalene,¹¹⁶ which are all substituted in the positions corresponding to the stronger influence of the methoxyl group. 3-Methylphenanthrene yields only the 6-acid on treatment with succinic anhydride,³⁹ but the



4-methylphenanthrene affords a small amount of the 1-isomer in addition to the 6-acid.³³ The few heterocyclic compounds that have been succinoylated are substituted in the expected positions.

Often the solvent or the reaction temperature affects the position of substitution or the ratio of isomers. When nitrobenzene is used as solvent, positions that are ordinarily subject to steric inhibition are usually avoided. This may be due to the formation of a bulky complex of nitrobenzene, aluminum chloride, and the anhydride, which finds an easier reaction path in a less blocked position.¹¹⁷ Bromination, nitration,

¹¹³ Haworth, Letsky, and Mavin, *J. Chem. Soc.*, **1932**, 1784.

¹¹⁴ Bachmann, Cronyn, and Struve, *J. Org. Chem.*, **12**, 596 (1947).

¹¹⁵ The 6-acid is probably the easiest to isolate. Orcutt and Bogert, *J. Am. Chem. Soc.*, **63**, 127 (1941), isolated 56% of the 6-acid and 38% of the more soluble 5-acid from the reaction between 2-methylnaphthalene and succinic anhydride. A mixture from which only the 6-acid was isolated in pure form is also obtained from 2-isopropylnaphthalene (ref. 112).

¹¹⁶ Haworth and Bolam, *J. Chem. Soc.*, **1932**, 2243.

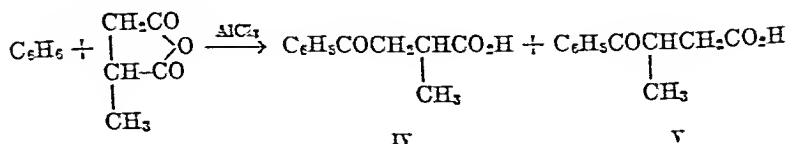
¹¹⁷ Royer, *Ann. chim.*, [12], **I**, 395 (1946); Royer and Bau-Hoi, *Compt. rend.*, **222**, 746 (1946).

¹¹⁸ Fieser, *Chemistry of Natural Products Related to Phenanthrene*, 2nd ed., p. 74, Reinhold Publishing Corp., New York, 1937.

and other reactions with naphthalene take place in the 1-position, whereas succinoylation of naphthalene in nitrobenzene solution yields appreciable amounts of the 2-isomer. Acetylation takes place in the 2-position when nitrobenzene is employed as solvent, but predominantly in the 1-position in carbon disulfide,¹¹³ which does not form a complex with aluminum chloride. The predominant formation of the 6-isomer in succinoylations of 2-alkylnaphthalenes appears to occur for the same reasons. 2-Methoxynaphthalene affords 9 parts of the 6-acid and 1 part of the 1-acid when the reaction is conducted in nitrobenzene. One group of workers has reported the formation of the 1-acid⁸⁴ when carbon disulfide is used as solvent, while another group has reported the formation of the 8-acid.^{84a} Benzene as a solvent is similar to carbon disulfide and unlike nitrobenzene. Two different acids are obtained in the succinoylation of chrysene, depending upon the solvent (nitrobenzene or benzene).^{53, 51} The use of higher temperatures increases the amount of the isomer that is produced to the smaller extent at low temperatures, as is always true in aromatic substitution reactions. Acenaphthene yields 87% of the 3-acid and 5% of the 1-acid at -15° , but at higher temperature more of the 1-acid is formed and the products become more difficult to purify.^{72, 112}

Substituted Succinic Anhydrides

The reaction between an aromatic compound and a monosubstituted succinic anhydride can proceed in two directions and result in the formation of two isomeric acids. Thus benzene and methylsuccinic anhydride can furnish α -methyl- β -benzoylpropionic acid (IV) and β -methyl- β -benzoylpropionic acid (V). Although many investigators isolated only



the α -methyl acid (IV),^{7, 123, 124} both isomers are actually produced.¹²⁵ The β -methyl acid is more difficult to isolate because it is formed to a

¹¹³ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, pp. 271-272, Reinhold Publishing Corp., New York, 1941.

¹¹⁴ Fieser, *Org. Syntheses*, 20, 1 (1940).

¹¹⁵ Klobb, *Bull. soc. chim. France*, [3] 23, 511 (1900).

¹¹⁶ Oppenheim, *Ber.*, 34, 4227 (1901).

¹¹⁷ Mayer and Stamm, *Ber.*, 56, 1424 (1923).

much smaller extent and is more soluble. The reaction between methylsuccinic anhydride and toluene also produces both possible isomers.¹²²

Naphthalene and methylsuccinic anhydride react to form two acids in which the acid chains are attached to the 1- and 2-positions of the naphthalene ring, respectively. Both acids correspond to type IV, with the methyl group farthest removed from the carbonyl group.⁶ The formation of the two other isomers (type V) is not reported. The preferential formation of the isomer in which the methyl group is directed away from the aromatic ring appears to be the rule with polynuclear hydrocarbons. Phenanthrene yields two acids of type IV with methylsuccinic anhydride through substitution in positions 2 and 3.¹²³ The 1- and 2-methylnaphthalenes are substituted in positions 4 and 6, respectively,^{113,124} to form two acids, which also belong to the α -methyl type (IV). When pyrene is condensed with methylsuccinic anhydride, the same type acid is obtained.^{47,125} It is possible that a very small amount of the other isomer (type V) is formed, but for all practical purposes polynuclear hydrocarbons and methylsuccinic anhydride produce only the corresponding α -methyl- β -aroylpropionic acids.

Substituted α -methyl- β -aroylpropionic acids (type IV) are also formed predominantly in the reaction between methylsuccinic anhydride and phenolic ethers or phenols. Anisole forms exclusively α -methyl- β -anisoylpropionic acid,¹²⁶ and the three cresol methyl ethers are also reported to yield only the α -methyl acids.¹²⁷ Veratrole, however, reacts with methylsuccinic anhydride to form both the α -methyl and β -methyl acids.^{128,129} Small amounts of the isomeric β -methyl- β -aroylpropionic acids are also formed in the methylsuccinoylation of resorcinol dimethyl ether and pyrogallol trimethyl ether, but the main product in both reactions is the α -acid.¹²⁸ Anisole has been condensed with mono-substituted succinic anhydrides in which the alkyl substituents varied from methyl to *n*-hexadecyl; only the α -alkyl- β -benzoylpropionic acid (type IV) was isolated.¹³⁰ Phenol is substituted in the 2-position, and the methyl group is again situated away from the benzene ring.¹²⁸

¹²² Cook and Haslewood, *J. Chem. Soc.*, **1934**, 423.

¹²³ Haworth, Mavin, and Sheldrick, *J. Chem. Soc.*, **1934**, 451.

¹²⁴ Bachmann and Carmack, *J. Am. Chem. Soc.*, **63**, 2494 (1941). See also Fieser and Herschberg, *J. Am. Chem. Soc.*, **60**, 1658 (1938), regarding the structure of this acid.

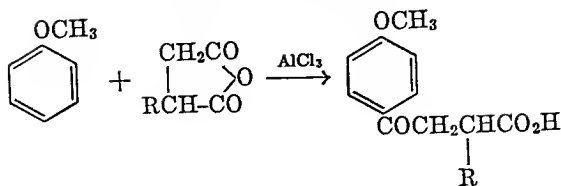
¹²⁵ Mitter and De, *J. Indian Chem. Soc.*, **36**, 199 (1939).

¹²⁶ Bhatt and Nargund, *J. Univ. Bombay*, **11**, Pt. 3, 131 (1942) [*C.A.*, **37**, 2000 (1943)].

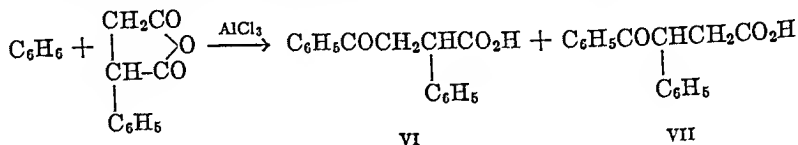
¹²⁷ Borsche and Niemann, *Ann.*, **502**, 264 (1933).

¹²⁸ Robertson and Water, *J. Chem. Soc.*, **1933**, 83.

¹²⁹ Mehta, Bokil, and Nargund, *J. Univ. Bombay*, **12A**, Pt. 3, 64 (1943) [*C.A.*, **38**, 2328 (1944)].



With phenylsuccinic anhydride or substituted phenylsuccinic anhydrides the ratio of isomeric α -phenyl and β -phenyl acids depends on the solvent. In the reaction between phenylsuccinic anhydride and benzene only β -phenyl- β -benzoylpropionic acid (VII) was isolated at first,¹³¹ but it was later shown that both acids (VI and VII) are formed in almost equal amounts when excess benzene is used as solvent.¹⁵ When the reaction is carried out in nitrobenzene, 89% of the α -phenyl acid (VI)



is produced and only 11% of the isomer.¹⁷ With toluene instead of benzene as reactant and diluent the acid corresponding to VII is formed to the extent of 77%, but in nitrobenzene solution the amounts are reversed and an 83% yield of α -phenyl- β -*p*-toluoylpropionic acid (type VI) is obtained. The effect of nitrobenzene on the ratio of isomeric acids formed when differently substituted phenylsuccinic anhydrides are condensed with benzene or toluene has been studied extensively with the results shown in Table I.¹⁷ Depending on the nature of the substituent in the *p*-position of the phenyl group, nitrobenzene seems to favor preferential formation of one isomer (see p. 233). The large amounts of acids of type VII obtained in some reactions seem to exclude steric hindrance as a factor determining the direction in which fission of the monosubstituted succinic anhydride occurs.

Mixtures of the two acids corresponding to VI and VII are also obtained when *o*- or *m*-cresyl methyl ether is condensed with *o*-methoxyphenylsuccinic anhydride,¹³² whereas *p*-methoxyphenylsuccinic anhydride forms only the α -isomer with the same two ethers.¹³³ The latter anhydride also forms only one isomer with the dimethyl ethers of the

¹³¹ Anschütz, Hahn, and Walter, *Ann.*, **354**, 150 (1907).

¹³² Mehta, Bokil, and Nargund, *J. Univ. Bombay*, **10**, Pt. 5, 137 (1942) [*C.A.*, **37**, 622 (1943)].

¹³³ Dalal, Bokil, and Nargund, *J. Univ. Bombay*, **8**, Pt. 3, 190 (1939) [*C.A.*, **34**, 2819 (1940)].

TABLE I

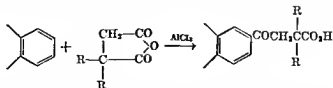
REACTION BETWEEN SUBSTITUTED PHENYLSUCCINIC ANHYDRIDES AND BENZENE OR TOLUENE ¹⁷

| A. Without a Solvent | | | |
|---|----------------------|---------------------|--------------------|
| Substituent in Succinic Anhydride | Aromatic Compound | α -Acid % | β -Acid % |
| Phenyl | Benzene | 48 | 52 |
| <i>p</i> -Nitrophenyl | Benzene | 45 | 55 |
| <i>p</i> -Methoxyphenyl | Benzene | Predominant | |
| <i>p</i> -Chlorophenyl | Benzene | 46 | 54 |
| Phenyl | Toluene | 23 | 77 |
| <i>p</i> -Nitrophenyl | Toluene | 20 | 80 |
| <i>p</i> -Methoxyphenyl | Toluene | 82 | 18 |

| B. Nitrobenzene as Solvent | | | |
|----------------------------|---------|-------------|-------------|
| Phenyl | Benzene | 89 | 11 |
| <i>p</i> -Nitrophenyl | Benzene | 5 | 95 |
| <i>p</i> -Methoxyphenyl | Benzene | Predominant | |
| <i>p</i> -Chlorophenyl | Benzene | | Predominant |
| Phenyl | Toluene | 83 | 17 |
| <i>p</i> -Nitrophenyl | Toluene | 33 | 67 |
| <i>p</i> -Methoxyphenyl | Toluene | Predominant | |

three dihydric phenols.¹²⁴ Only the α -isomer is formed in the condensation of veratrole with phenylsuccinic anhydride,¹²⁵ but biphenyl reacts with phenylsuccinic anhydride with the formation of the β -acid as the principal reaction product.¹²⁶

Unsymmetrically substituted succinic anhydrides having two substituents on the same carbon atom, such as α,α -dimethyl- or α,α -diethylsuccinic anhydride, invariably react so as to form the α,α -dialkyl- β -aroylpropionic acid as the sole product. This has been demonstrated in

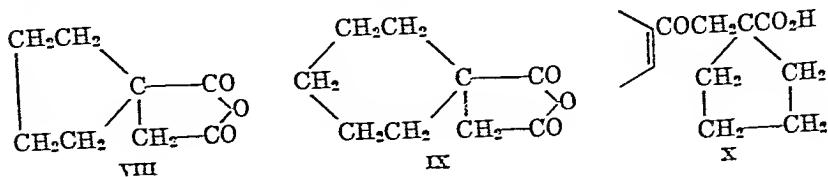


¹²⁴ Savkar, Bokil, and Nargund, *J. Univ. Bombay*, **8**, Pt. 3, 193 (1939) [*C.A.*, **34**, 2820 (1940)]. Guaiacol and hydroquinone monomethyl ether do not react with *p*-methoxyphenylsuccinic anhydride. For the failure of these compounds to react with succinic anhydride see ref. 22. *p*-Methoxyphenylsuccinic anhydride was at first reported not to react very smoothly with veratrole. See Robinson and Walker, *J. Chem. Soc.*, 1935, 1530.

¹²⁵ Robinson and Young, *J. Chem. Soc.*, 1935, 1414.

¹²⁶ Price and Tomisek, *J. Am. Chem. Soc.*, **65**, 439 (1943).

the reaction of α,α -dimethylsuccinic anhydride with benzene,^{14, 15, 18, 137, 138} toluene,¹³³ naphthalene,¹³³ α -methylnaphthalene,¹³³ and hydrindene⁵⁵ and also in the condensation of α,α -diethylsuccinic anhydride with benzene.¹³³ With naphthalene two acids are produced (1- and 2-position), but fission of the anhydride always occurs in such a way that the *gem*-dialkyl group is farthest away from the aromatic ring.¹²³ The same generalization also holds for the reaction between benzene or naphthalene and α -methyl- α -ethylsuccinic anhydride.^{127, 129} Certain more complex anhydrides, such



as VIII and IX, which can be considered unsymmetrically substituted succinic anhydrides, have been condensed with benzene, toluene, ethylbenzene, hydrindene, naphthalene, and methylnaphthalene.^{14, 15, 141, 142, 143} All the acids obtained are of type X, with the cyclic substituent away from the aromatic ring.

The reactions between α,β -dimethylsuccinic anhydride and benzene,¹³ and α,β -diethylsuccinic anhydride and anisole,¹⁴⁴ give the corresponding α,β -dialkylaroylpropionic acids in 86% and 91% yield, respectively. The formation of stereoisomers has not been observed; *cis*- and *trans*-dimethylsuccinic anhydride yield the same acid when condensed with veratrole.¹⁴⁵ In the reaction between trimethylsuccinic anhydride and benzene, α,α,β -trimethylbenzoylpropionic acid is obtained in good yield,¹³ but tetramethylsuccinic anhydride cannot be used in the preparation of keto acids.¹⁵ Carbon monoxide is evolved during the reaction, and the product obtained is in all probability $\alpha,\alpha,\beta,\beta$ -tetramethyl- β -phenylpropionic acid (XI). Tetramethylsuccinic anhydride reacts

¹³ Clemo and Dickenson, *J. Chem. Soc.*, 1937, 255.

¹³³ Sengupta, *J. prakt. Chem.*, [2] 151, 82 (1935).

¹³⁷ Sengupta, *J. prakt. Chem.*, [2] 152, 9 (1939).

¹³⁸ Barker and Clemo, *J. Chem. Soc.*, 1940, 1277.

¹⁴¹ Sengupta, *J. Indian Chem. Soc.*, 16, 349 (1939).

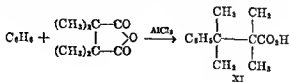
¹⁴² Sengupta, *J. Indian Chem. Soc.*, 17, 101 (1940); *Current Sci.*, 5, 295 (1936) [*C.A.*, 31, 2587 (1937)].

¹⁴³ Sengupta, *J. Indian Chem. Soc.*, 17, 183 (1940); *Science and Culture*, 3, 56 (1937) [*C.A.*, 31, 7868 (1937)].

¹⁴⁴ Baker, *J. Am. Chem. Soc.*, 65, 1572 (1943).

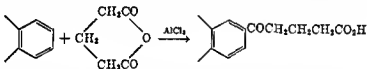
¹⁴⁵ Haworth and Marvin, *J. Chem. Soc.*, 1932, 1455.

similarly with toluene. Reactions with loss of carbon monoxide are general with anhydrides of tertiary carboxylic acids.^{148, 147}



Glutaric Anhydride and Substituted Glutaric Anhydrides

Only a few reactions between glutaric anhydride and an aromatic compound have been carried out. The products are γ -aroylbutyric acids, but the formation of a small amount of the corresponding diketone ($\text{ArCOCH}_2\text{CH}_2\text{CH}_2\text{COAr}$) has been observed in at least two reactions.^{148, 149} The formation of diketones may be found to be more general if the reaction with glutaric anhydride is studied in more detail. From



the scanty data that are available the yield in the reaction between glutaric anhydride and an aromatic compound appears to be lower than in the corresponding reaction with succinic anhydride. The reaction between glutaric anhydride and acenaphthene in nitrobenzene solution is described as particularly poor, by contrast with the condensation with succinic anhydride.¹⁴ Benzene,^{15, 148} toluene,¹⁴⁸ anisole,^{38, 150, 151} phenetole,^{150, 142} chlorobenzene,³⁰ veratrole,¹⁵² thiophene,¹⁵⁴ tetralin,³⁶ pyrogallol trimethyl ether,¹⁵⁵ and acenaphthene³⁹ have been converted into the respective γ -aroylbutyric acids. The point of attack on the aromatic ring is the same as with the lower homolog.

Some β,β -dialkylglutaric anhydrides have been successfully condensed with benzene, but β -phenylglutaric anhydride did not react in the ex-

¹⁴⁸ Laughlin and Whitmore, *J. Am. Chem. Soc.*, **54**, 4463 (1932).

¹⁴⁷ Whitmore and Crooks, *J. Am. Chem. Soc.*, **60**, 2078 (1938).

¹⁴⁹ Borsche and Sinn, *Ann.*, **538**, 283 (1939).

¹⁵⁰ Carter, Simonsen, and Williams, *J. Chem. Soc.*, **1940**, 451.

¹⁵¹ Plant and Tomlinson, *J. Chem. Soc.*, **1935**, 856.

¹⁵² van der Zanden, *Rec. trav. chim.*, **57**, 242 (1938).

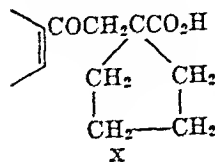
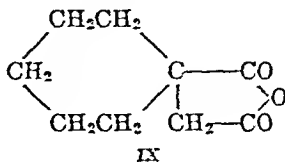
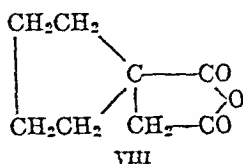
¹⁵³ van der Zanden, *Rec. trav. chim.*, **58**, 181 (1939).

¹⁵⁴ Haworth and Atkinson, *J. Chem. Soc.*, **1938**, 797.

¹⁵⁵ Cagniant and Deluzarche, *Compt. rend.*, **222**, 1301 (1946).

¹⁵⁶ Haworth, Moore, and Pauson, *J. Chem. Soc.*, **1943**, 1045.

the reaction of α,α -dimethylsuccinic anhydride with benzene,^{14, 16, 18, 137, 138} toluene,¹³⁸ naphthalene,¹³⁷ α -methylnaphthalene,¹³⁷ and hydrindene¹⁶ and also in the condensation of α,α -diethylsuccinic anhydride with benzene.¹³⁸ With naphthalene two acids are produced (1- and 2-position), but fission of the anhydride always occurs in such a way that the *gem*-dialkyl group is farthest away from the aromatic ring.¹³⁷ The same generalization also holds for the reaction between benzene or naphthalene and α -methyl- α -ethylsuccinic anhydride.^{137, 138} Certain more complex anhydrides, such



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The reactions between α,β -dimethylsuccinic anhydride and benzene,¹³ and α,β -diethylsuccinic anhydride and anisole,¹⁴⁴ give the corresponding α,β -dialkylaroylpropionic acids in 86% and 91% yield, respectively. The formation of stereoisomers has not been observed; *cis*- and *trans*-dimethylsuccinic anhydride yield the same acid when condensed with veratrole.¹⁴⁵ In the reaction between trimethylsuccinic anhydride and benzene, α,α,β -trimethylbenzoylpropionic acid is obtained in good yield,¹³ but tetramethylsuccinic anhydride cannot be used in the preparation of keto acids.¹³ Carbon monoxide is evolved during the reaction, and the product obtained is in all probability $\alpha,\alpha,\beta,\beta$ -tetramethyl- β -phenylpropionic acid (XI). Tetramethylsuccinic anhydride reacts

¹³⁷ Clemo and Dickenson, *J. Chem. Soc.*, 1937, 255.

¹³⁸ Sengupta, *J. prakt. Chem.*, [2] 151, 82 (1935).

¹³⁹ Sengupta, *J. prakt. Chem.*, [2] 152, 9 (1939).

¹⁴⁰ Barker and Clemo, *J. Chem. Soc.*, 1940, 1277.

¹⁴¹ Sengupta, *J. Indian Chem. Soc.*, 16, 349 (1939).

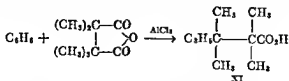
¹⁴² Sengupta, *J. Indian Chem. Soc.*, 17, 101 (1940); *Current Sci.*, 5, 295 (1936) [*C.A.*, 31, 2557 (1937)].

¹⁴³ Sengupta, *J. Indian Chem. Soc.*, 17, 153 (1940); *Science and Culture*, 3, 56 (1937) [*C.A.*, 31, 7865 (1937)].

¹⁴⁴ Baker, *J. Am. Chem. Soc.*, 65, 1572 (1943).

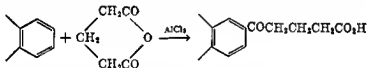
¹⁴⁵ Haworth and Marvin, *J. Chem. Soc.*, 1932, 1435.

similarly with toluene. Reactions with loss of carbon monoxide are general with anhydrides of tertiary carboxylic acids.^{146, 147}



Glutaric Anhydride and Substituted Glutaric Anhydrides

Only a few reactions between glutaric anhydride and an aromatic compound have been carried out. The products are γ -aroylbutyric acids, but the formation of a small amount of the corresponding diketone ($\text{ArCOCH}_2\text{CH}_2\text{CH}_2\text{COAr}$) has been observed in at least two reactions.^{148, 149} The formation of diketones may be found to be more general if the reaction with glutaric anhydride is studied in more detail. From



the scanty data that are available the yield in the reaction between glutaric anhydride and an aromatic compound appears to be lower than in the corresponding reaction with succinic anhydride. The reaction between glutaric anhydride and acenaphthene in nitrobenzene solution is described as particularly poor, by contrast with the condensation with succinic anhydride.³⁹ Benzene,^{15, 148} toluene,¹⁴⁹ anisole,^{34, 150, 151} phenetole,^{150, 152} chlorobenzene,³⁹ veratrole,¹⁵³ thiophene,¹⁵⁴ tetralin,³⁵ pyrogallol trimethyl ether,¹⁵⁵ and acenaphthene³⁹ have been converted into the respective γ -aroylbutyric acids. The point of attack on the aromatic ring is the same as with the lower homolog.

Some β,β -dialkylglutaric anhydrides have been successfully condensed with benzene, but β -phenylglutaric anhydride did not react in the ex-

¹⁴⁶ Laughlin and Whitmore, *J. Am. Chem. Soc.*, **54**, 4463 (1932).

¹⁴⁷ Whitmore and Crooks, *J. Am. Chem. Soc.*, **60**, 2078 (1938).

¹⁴⁸ Borsche and Sinn, *Ann.*, **533**, 283 (1939).

¹⁴⁹ Carter, Simonsen, and Williams, *J. Chem. Soc.*, **1940**, 451.

¹⁵⁰ Plant and Tomlinson, *J. Chem. Soc.*, **1935**, 856.

¹⁵¹ van der Zanden, *Rec. trav. chim.*, **57**, 242 (1938).

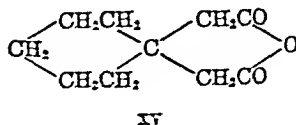
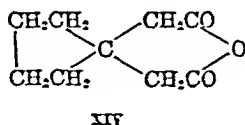
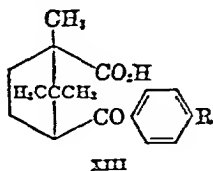
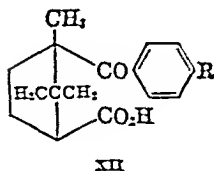
¹⁵² van der Zanden, *Rec. trav. chim.*, **58**, 181 (1939).

¹⁵³ Haworth and Atkinson, *J. Chem. Soc.*, **1938**, 797.

¹⁵⁴ Cagniant and Deluzarche, *Compt. rend.*, **222**, 1301 (1946).

¹⁵⁵ Haworth, Moore, and Pauson, *J. Chem. Soc.*, **1943**, 1045.

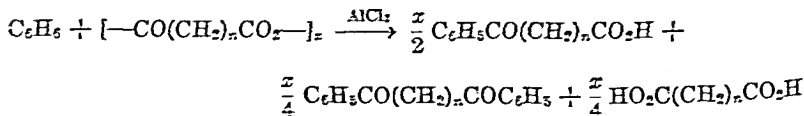
pected manner; instead it formed ketohydrindene-3-acetic acid by an internal condensation.^{15, 156} Camphoric anhydride, which can be considered to be a completely alkylated glutaric anhydride like tetramethylsuccinic anhydride, loses carbon monoxide when treated with aluminum chloride.^{157, 158, 159} However, camphoric anhydride with toluene¹⁶⁰ or anisole¹⁶⁰ yields the corresponding aroylcamphoric acid (XII or XIII).



The disubstituted glutaric anhydrides XIV and XV, on treatment with benzene or toluene in the presence of aluminum chloride, furnish the expected acids.¹⁵

Polymeric Anhydrides of Higher Dibasic Acids

The polymeric anhydrides of adipic and sebacic acid can be employed in the Friedel and Crafts synthesis of keto acids.¹⁵¹ With benzene as reactant and solvent, ω -benzoylvaleric and ω -benzoylpelargonic acid are obtained in 75 and 78% yields, respectively. The reaction does not yield an aroylaliphatic acid exclusively but follows the course outlined in the equation to furnish dibasic acid and diketone as well. The yields



¹⁵⁶ Internal cyclization of phenylethylsuccinic anhydride could not be effected, *Bergs. Ber.*, 63, 1294 (1930), but benzylsuccinic anhydrides cyclize readily under the influence of aluminum chloride with the formation of 1-tetralone-3-carboxylic acids. Haworth, Jones, and Way, *J. Chem. Soc.*, 1943, 10.

¹⁵⁷ Lees and Perkin, *J. Chem. Soc.*, 79, 356 (1901).

¹⁵⁸ Perkin and Yates, *J. Chem. Soc.*, 79, 1373 (1901).

¹⁵⁹ Burcker, *Bull. soc. chim. France*, [3] 4, 112 (1890); [3] 13, 901 (1895).

¹⁶⁰ Eykman, *Chem. Weekblad*, 4, 727 (1907) (*Chem. Zentr.*, 1907, II, 2046).

¹⁶¹ Hill, *J. Am. Chem. Soc.*, 54, 4105 (1932).

quoted are based on this equation. In the above reactions the yields of diketones are 85% and 86%, respectively. Although only a few examples have been recorded, this reaction should be applicable to many other aromatic compounds as well as to anhydrides of other dibasic acids. Anisole and phenetole have been condensed with the polymeric anhydride of adipic acid.¹⁶² The reaction between thiophene and the polymeric anhydrides of adipic, suberic, azelaic, and sebacic acid results in the formation of the respective thenoyl fatty acids in 3.8%, —%,¹⁶³ 24.5%, and 8.3% yield.¹⁶⁴ Yields of 0%, 29.8%, 27%, and 21.2% of the diketones were secured.¹⁶⁴ All the yields are based on the equation above. These yields are fairly low, and, in spite of the fact that the polymeric anhydrides are easily prepared, the Friedel and Crafts reaction with the ester acid chlorides of the acids might often be preferable. (See Table II, p. 253.)

Maleic Anhydride and Substituted Maleic Anhydrides

The interest in β -aroyleacrylic acids, obtained from maleic anhydride and an aromatic compound in the presence of aluminum chloride, has not been so great as that in the β -aroylepropionic acids. Such interest as there has been has centered chiefly around the stereochemistry of the acids¹⁶⁵⁻¹⁶⁹ and the structure of the so-called "Pechmann dyes," colored substances obtained when benzoylacrylic acids are heated with dehydrating agents.^{2, 17, 170} Benzoylacrylic acids have been utilized as starting materials in a synthesis of anthraquinone derivatives.¹⁷¹ The reaction between aromatic compounds and maleic anhydride has generally given lower yields and less pure products than the comparable reaction with succinic anhydride. Consequently many chemists have preferred to prepare the acrylic acids by elimination of hydrogen bromide from the

¹⁶² Plant and Tomlinson, *J. Chem. Soc.*, **1935**, 1092.

¹⁶³ The product resulting from the reaction of suberic anhydride was not obtained in a solid state.

¹⁶⁴ Billman and Travis, *Proc. Indiana Acad. Sci.*, **54**, 101 (1945) [*C.A.*, **40**, 1826 (1946)].

¹⁶⁵ Benzoylacrylic acid, obtained by the general Friedel and Crafts reaction, has the *trans* configuration as a result of an isomerization brought about by the catalyst. By analogy, the same configuration might be expected whenever maleic anhydride itself is condensed with aromatic compounds. However, dibromomaleic anhydride forms the *cis* acid with benzene and mesitylene; and dimethylmaleic anhydride forms the *cis* acid with benzene and biphenyl, but the *trans* acid with mesitylene. See Lutz and co-workers, refs. 166-169.

¹⁶⁶ Lutz, *J. Am. Chem. Soc.*, **52**, 3405 (1930).

¹⁶⁷ Lutz and Taylor, *J. Am. Chem. Soc.*, **55**, 1168 (1933).

¹⁶⁸ Lutz and Taylor, *J. Am. Chem. Soc.*, **55**, 1593 (1933).

¹⁶⁹ Lutz and Couper, *J. Org. Chem.*, **6**, 77 (1941).

¹⁷⁰ Bogert and Rutter, *Proc. Natl. Acad. Sci. U.S.*, **10**, 363 (1924).

¹⁷¹ Fieser and Fieser, *J. Am. Chem. Soc.*, **57**, 1679 (1935).

corresponding bromopropionic acids, which can be readily obtained by direct bromination of the propionic acids.^{39, 172-175} More careful study of the reaction between maleic anhydride and alkylated benzenes¹⁷¹ and certain phenolic ethers¹⁷⁶ has led to purer products in better yield. An extension of these studies to reactions of maleic anhydride with other aromatic compounds has resulted in comparable improvements.^{176a}

A reasonably large number of aromatic compounds have been condensed with maleic anhydride. Substitution occurs generally in the expected position with the formation of only one isomer. From the reaction between maleic anhydride and naphthalene two acids have been isolated (substitution in the 1- and the 2-positions).¹⁷⁷ Anthracene, in contrast to its behavior on succinoylation, is reported to form the 9-acid,¹⁷⁸ but no proof of structure is given. The reaction between maleic anhydride and polynuclear hydrocarbons in nitrobenzene solution has been reported to give particularly poor results, despite contrary claims in the patent literature.³⁹ Acenaphthene forms the corresponding acid in only 32% yield, whereas in succinoylation a yield of about 85% is easily secured. No product could be isolated when naphthalene was used with nitrobenzene as solvent.

In the early investigations of the reaction between the alkylbenzenes and maleic anhydride, the alkylbenzenes were used both as reactant and solvent and the yields of pure products were very low.^{179, 180} More recent work has shown that alkylbenzenes can readily be condensed with maleic anhydride in 60-70% yields in tetrachloroethane solution.¹⁷¹ Good yields are obtained in the reaction of maleic anhydride with the cresol methyl ethers, veratrole, and hydroquinone dimethyl ether when nitrobenzene is employed as the solvent.¹⁷⁶ Reaction in carbon disulfide gives lower yields. Diphenyl ether also reacts with maleic anhydride,¹⁸¹ as does anisole,^{171, 176} phenetole,^{72, 179} and phenol itself.¹⁷⁷ Resorcinol dimethyl ether, however, forms the expected acid (XVI) only to a small extent.¹⁸² The main product of the reaction is a substituted succinic anhydride (XVII) formed by addition of resorcinol dimethyl ether to

¹⁷² Bougault, *Ann. chim.*, [8] 15, 498 (1908).

¹⁷³ Kohler and Engelbrecht, *J. Am. Chem. Soc.*, 41, 764 (1919).

¹⁷⁴ Rice, *J. Am. Chem. Soc.*, 45, 222 (1923).

¹⁷⁵ Rice, *J. Am. Chem. Soc.*, 46, 214 (1924).

¹⁷⁶ Dave and Nargund, *J. Univ. Bombay*, 7, Pt. 3, 191 (1938) [*C.A.*, 33, 3779 (1939)].

^{176a} Papa, Schwenk, Villani, and Klingsberg, *J. Am. Chem. Soc.*, 70, 3356 (1948).

¹⁷⁷ Bogert and Ritter, *J. Am. Chem. Soc.*, 47, 526 (1925).

¹⁷⁸ Oddy, *J. Am. Chem. Soc.*, 45, 2156 (1923).

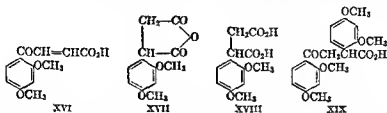
¹⁷⁹ Kozniewski and Marchlewski, *Bull. Acad. Sci. Cracow*, 81 (1906) (*Chem. Zentr.*, 1906, II, 1189).

¹⁸⁰ Kozak, *Bull. Acad. Sci. Cracow*, 407 (1906) (*Chem. Zentr.*, 1907, I, 1788).

¹⁸¹ Rice, *J. Am. Chem. Soc.*, 48, 269 (1926).

¹⁸² Rice, *J. Am. Chem. Soc.*, 53, 3153 (1931).

maleic anhydride. The anhydride (XVII) is partly hydrolyzed to the substituted succinic acid (XVIII). A fourth product is the acid XIX, formed by addition of the ether to the acrylic acid XVI. A similar

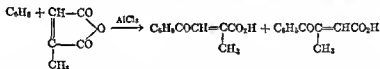


addition has been observed with maleic anhydride and benzene in the presence of excess aluminum chloride.¹³³ The product, α -phenyl- β -



benzoylpropionic acid (XX), is also obtained when benzene is condensed with β -benzoylacrylic acid in the presence of aluminum chloride. Toluene behaves similarly.

The reaction with methylmaleic anhydride and benzene, like the corresponding reaction with methylsuccinic anhydride, was first reported to yield only one isomer.^{2,177} Actually both α -methyl- and β -methylbenzoylacrylic acid are formed.^{125,134} Two acids are also obtained from



the reaction between bromomaleic anhydride and benzene.¹³⁵ Dimethylmaleic anhydride has been successfully condensed with benzene,¹⁶⁸ mesitylene,¹⁵³ biphenyl,¹⁶⁹ and bromobenzene,¹⁶⁹ while dibromomaleic anhydride has been condensed with benzene and mesitylene.¹⁶⁶ Maleic anhydride reacts with hydroquinone, hydroquinone methyl ethers, or their substituted derivatives in a sodium chloride-aluminum chloride

¹³³ Pummerer and Buchta, *Ber.*, 69, 1005 (1936).

¹³⁴ The stereochemical configuration of the acids from methylmaleic anhydride and benzene is not known. However, with bromobenzene, instead of benzene, the resulting β -methyl- β -p-bromobenzoylacrylic acid has the *cis* configuration, whereas the α -methyl- β -p-bromobenzoylacrylic acid is *trans*. See ref. 167.

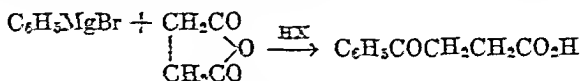
¹³⁵ Rice, *J. Am. Chem. Soc.*, 52, 2094 (1930).

melt at temperatures above 200° with the formation of naphthazarins.^{156,157} The reaction has been used extensively, but a detailed description is beyond the scope of this chapter.

Other Synthetic Methods

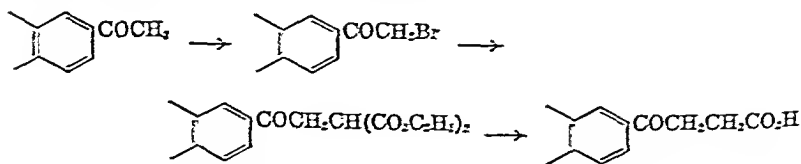
In addition to the synthesis from an aromatic hydrocarbon, succinic anhydride or a substituted succinic anhydride, and aluminum chloride, β -aroylpropionic acids can be prepared by two other methods: the Grignard reaction between succinic anhydride or a substituted succinic anhydride and an arylmagnesium halide,¹⁵³ and the stepwise elaboration of the side chain in an aryl ketone.

The first method suffers from the disadvantage that the yields are generally low, although satisfactory yields have been obtained with dimethylsuccinic anhydride.¹⁵³ The advantage of this method is that



the point of attachment of the side chain is determined by the location of the halogen in the aryl halide; this permits the succinic acid side chain to be attached to positions that may not be available through the direct Friedel and Crafts synthesis.

The second method usually starts with a methyl aryl ketone, which is brominated and then condensed with sodium malonic ester. Hydrolysis and decarboxylation furnish the arylpropionic acid. This method is obviously more laborious than the Friedel and Crafts reaction, but it



has been used frequently where acetylation and succinylation do not occur at the same position in an aromatic nucleus or for the proof of structure of acids obtained by succinylation. If an aryl ethyl ketone is

¹⁵⁶ Zahn and Ochwat, *Ann.*, 462, 72 (1925).

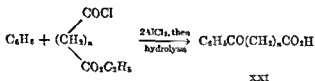
¹⁵⁷ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, pp. 581-582, Reinhold Publishing Corp., New York, 1941.

¹⁵³ Weizmann, Blum-Bergmann, and Bergmann, *J. Chem. Soc.*, 1935, 1370; Weizmann and Pickles, *Proc. Roy. Soc. London*, 20, 291 (1904); Komppa and Rohrmann, *Ann.*, 509, 259 (1934).

¹⁵² Fieser and Dault, *J. Am. Chem. Soc.*, 63, 782 (1941).

used, β -methyl- β -aroylpropionic acids (which are less accessible by direct succinylation) can be obtained. If methylmalonic ester is used, α -methyl- β -aroylpropionic acids can be prepared.

The reaction between an aromatic hydrocarbon and succinoyl dichloride or the ester acid chloride of succinic acid has been used only in single instances for the preparation of β -aroylpropionic acids.^{190, 191} However, the ester acid chlorides of the higher homologs of succinic acid seem superior to the corresponding polymeric anhydrides for the synthesis of ω -aroylaliphatic acids such as XXI, where $n > 2$.^{58, 191a} The



ester acid chlorides are prepared easily,^{191a, 192} and the final products are obtained in much better yields and greater purity. The more direct preparation of the polymeric anhydrides is offset by the fact that only one-half of the available anhydride is converted into the keto acid, which

TABLE II

COMPARISON OF ESTER ACID CHLORIDES WITH ACID ANHYDRIDES IN THE PREPARATION OF ω -AROYLALIPHATIC ACIDS

| Aromatic Compound | Ester Acid Chloride | Yield % | Reference | Anhydride | Yield % | Reference |
|-------------------|---------------------|------------|-----------|-------------|---------|-----------|
| Anisole | Glutaric | 93.5 | 191a | Glutaric | 85 | 36 |
| Thiophene | Glutaric | 75 | 154 | Glutaric | 39.4 | 154 |
| Tetralin | Glutaric | 71 | 36 | Glutaric | 43 | 36 |
| Benzene | Adipic | 55, 78 | 36, 191a | Polyadipic | 75 | 161 |
| Anisole | Adipic | 66, 95 | 36, 191a | Polyadipic | 43 | 162 |
| Thiophene | Adipic | 37.6, 70 * | 36, 191a | Polyadipic | 3.8 † | 164 |
| Benzene | Sebacic | 80 | 36, 191a | Polysebacic | 78 | 161 |
| Thiophene | Sebacic | 25, 66 * | 36, 191a | Polysebacic | 8.3 † | 164 |

* Stannic chloride was used as the condensing agent; with aluminum chloride the yields were between 30% and 40%.

† Stannic chloride was used as the condensing agent.

¹⁹⁰ Claus, *Ber.*, 20, 1374 (1887).

¹⁹¹ Fager, *J. Am. Chem. Soc.*, 67, 2217 (1945).

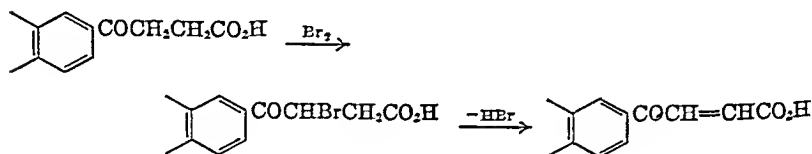
^{191a} Papp, Schwenk, and Hankin, *J. Am. Chem. Soc.*, 69, 3013 (1947).

¹⁹² *Org. Syntheses, Coll. Vol. 2*, 276 (1943); *Org. Syntheses*, 25, 19, 71 (1945).

makes the procedure less suitable for larger-scale preparations. For small-scale preparations, and when one of the reactants, e.g., benzene, can be used as solvent, the quicker preparation through the polymeric anhydrides has its advantages. Table II supports the statement that better yields are obtained with the ester acid chlorides than with the polymeric anhydrides or with glutaric anhydride.

The same acids that are now accessible through the use of either the polymeric anhydrides or the ester acid chlorides were previously obtained only as by-products in the reaction of the aromatic compounds with the acid dichlorides^{193,194} or through stepwise elaboration of the side chain by standard procedures.

The alternative method for the preparation of β -benzoylacrylic acids was mentioned earlier. This method starts with the β -benzoylpropionic acids obtained from succinic anhydride and an aromatic compound.



Bromination, followed by elimination of hydrobromic acid, usually gives the unsaturated acid in good yield, and many investigators have prepared β -aroylacrylic acids by this method rather than by the Friedel and Crafts reaction with maleic anhydride.^{33, 172-175}

EXPERIMENTAL CONDITIONS

The usual precautions of a Friedel and Crafts reaction must be observed, particularly with regard to the anhydrous conditions of catalyst and reactants.¹⁹⁵ Solvents should be of good grade, and benzene should be sulfur free. Finely divided aluminum chloride is preferable to coarsely ground material (lumps), although very finely powdered material may lead to too rapid a reaction, often undesirable with sensitive compounds. When a solvent is used in which aluminum chloride is soluble (nitrobenzene or tetrachloroethane), the particle size is not of too great importance, but large lumps should always be avoided.

The permissible variations in carrying out the reaction include the solvent, the temperature, the reaction time, and the order of addition

¹⁹³ Etax, *Ann. chim.*, [7] 9, 391 (1896).

¹⁹⁴ Borsche, *Ber.*, 52, 2079 (1919).

¹⁹⁵ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, pp. 867 ff., Reinhold Publishing Corp., New York, 1941.

of reagents. Of these the choice of the proper solvent is probably the most important, because this often determines the yield and the purity of the product and in some reactions also the point of substitution. The usual solvents are carbon disulfide, benzene, nitrobenzene, and *sym*-tetrachloroethane. If the compound to be substituted is readily available and cheap, such as benzene or toluene, it can be used in excess as solvent. The use in excess of more highly substituted liquid alkylbenzenes or phenolic ethers is not recommended although it has been reported. The early investigators appear to have employed carbon disulfide or benzene in preference to other solvents, but these solvents have been replaced most advantageously by nitrobenzene, tetrachloroethane, or a mixture of the two.

Aluminum chloride has a definite destructive action on many polynuclear aromatic hydrocarbons, their phenolic ethers, and some heterocyclic compounds such as thiophene.¹⁹⁶ Nitrobenzene and tetrachloroethane both dissolve aluminum chloride and form complexes with it; the catalytic activity and the destructiveness of the catalyst are decreased by complex formation with the solvent.^{196, 198} Carbon disulfide, benzene, and ligroin do not dissolve aluminum chloride to any appreciable extent, and the compound to be substituted is exposed to the destructive influence of the catalyst throughout most of the reaction (unless the compound itself, for example chlorobenzene, forms a complex with aluminum chloride). It follows then that for sensitive compounds, and all polynuclear hydrocarbons belong to this group, nitrobenzene or tetrachloroethane should be employed as solvents.

Carbon disulfide may be used with compounds such as the halobenzenes that contain deactivating groups. Prolonged heating is then necessary. But the yields are usually not high, and if the halobenzenes are readily available it is probably preferable to use them in excess without a diluent. When comparisons were made to determine the effect of different solvents, carbon disulfide was usually found to result in the lowest yield. Nitrobenzene does not appear to be a good solvent for succinoylation of halogenated benzenes,^{36, 96, 98} possibly because the catalytic activity of aluminum chloride in solution is too low.

Although nitrobenzene is the most adequate solvent for polynuclear hydrocarbons, alkylated benzenes are best succinoylated in *sym*-tetrachloroethane solution.³³ This solvent proved to be more suitable than carbon disulfide, benzene, ligroin, or nitrobenzene, but was unsuitable for naphthalene. The yields usually range between 80% and 90%.

¹⁹⁶ Fieser, *Experiments in Organic Chemistry*, 2nd ed., p. 413, D. C. Heath and Co., Boston, 1941.

¹⁹⁸ Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, pp. 210-211, 873, Reinhold Publishing Corp., New York, 1941.

For phenolic ethers in both the benzene and naphthalene series, nitrobenzene and tetrachloroethane have been employed with good success. Usually nitrobenzene gives the higher yields, but sometimes this is reversed (see Table III). Benzene has also been used as solvent, but it is not so generally applicable as the other solvents mentioned. With carbon disulfide the yields are low throughout. Some of the results on the succinylation of the methyl ethers of dihydric phenols are summarized in Table III.

TABLE III =

EFFECT OF THE SOLVENT ON THE YIELD OF β -AROYLPROPIONIC ACIDS FROM THE DIMETHYL ETHERS OF THE DIHYDROXYBENZENES

| Aromatic Compound | Yield of β -Aroylpropionic Acid in | | |
|-----------------------------|--|-------------------------------|--------------|
| | Carbon Disulfide | <i>sym</i> -Tetrachloroethane | Nitrobenzene |
| | % | % | % |
| Resorcinol dimethyl ether | 50 | 60 | 88 |
| Catechol dimethyl ether | 45 | 64 | 44 |
| Hydroquinone dimethyl ether | 40 | 45 | 70 |

The best solvent for the succinylation of aromatic ethers, however, appears to be a mixture of tetrachloroethane (80%) and nitrobenzene (20%).⁷¹ This mixture can be employed in large runs, where nitrobenzene has been found to have some undesirable oxidative action;²⁴ yields of 80–90% and often more are usually secured.¹²⁷ A 95% yield of β -*p*-anisoylpropionic acid was obtained by several investigators with as much as three moles of anisole.^{74, 124, 129} The mixed solvent is particularly useful for aromatic ethers containing a naphthyl group. The yields from the reaction of 1,5-dimethoxynaphthalene and succinic anhydride are summarized in Table IV. The mixed solvent has also proved useful in the succinylation of compounds other than ethers, for example, ethylbenzene,²⁰ hydrindene,²⁵ diphenylene oxide,¹²¹ and phenylcyclohexane.²⁶

Benzene, which can be used as solvent only for those compounds that are more reactive than itself, is generally employed in all reactions where it is one of the reactants. In the reaction between dimethylmaleic

⁷¹ Fieser and Herzberg, ref. 71, report that the acid from veratrole and succinic anhydride is formed in a yield of 46% in carbon disulfide, 73% in nitrobenzene, and 67% in the mixture of nitrobenzene and tetrachloroethane. The product obtained with the solvent mixture is purest. Haworth and Marvin, ref. 145, obtained an 85% yield using nitrobenzene. An 84% yield of the acid was later secured by Holmes and Mann, ref. 252, who employed the solvent mixture. See also ref. 275.

¹²⁶ Plimmer, Short, and Hill, *J. Chem. Soc.*, 1938, 695.

¹²⁷ Price and Kaplan, *J. Am. Chem. Soc.*, 66, 447 (1944).

²⁵ Baidar and Warren, *J. Chem. Soc.*, 1939, 944.

TABLE IV
SUCCINOYLATION OF 1,5-DIMETHOXYNAPHTHALENE

| Solvent | Yield % | Reference |
|--|------------|-----------|
| Carbon disulfide | 21 | 24 |
| Tetrachloroethane | 80 * | 24 |
| Nitrobenzene | 85 | 24 |
| Mixture of nitrobenzene and tetrachloroethane | 93 † | 87 |

* This reaction was run at 74°, and partial demethylation took place.

† When three equivalents of aluminum chloride were used the yield was 98%.

anhydride and benzene, however, better results were obtained when carbon disulfide was the diluent.^{16a} Although inferior to nitrobenzene and tetrachloroethane for reactions involving polynuclear hydrocarbons, benzene has been found to be an excellent solvent for certain benzene derivatives containing alicyclic rings, such as tetralin,¹⁷ fluorene,¹⁸ and also diphenyl ether and diphenyl sulfide,^{24, 25} but not hydrindene or acenaphthene.²⁰ Benzene is also the most suitable solvent for the succinoylation of retene and is superior to nitrobenzene.^{43, 49}

Table V, summarizing the results in the literature, suggests the solvents which may be most advantageously employed for the succinoylation of several classes of compounds.

TABLE V
PREFERRED SOLVENTS FOR SUCCINOYLATION

| Type of Compound to Be Succinoylated | Solvent |
|---|--|
| Benzene | Benzene |
| Alkylbenzenes | Tetrachloroethane |
| Phenols | Tetrachloroethane |
| Aromatic ethers | Nitrobenzene, tetrachloroethane, or, best, a mixture of the two |
| Halogenated benzenes | Carbon disulfide or excess reactant * |
| Benzene with alicyclic rings | Benzene |
| Polynuclear hydrocarbons | Nitrobenzene |

* The use of excess reactant as solvent in the succinoylation of iodobenzene does not appear to be suitable.

For anhydrides other than succinic anhydride or its derivatives, the data are not sufficiently numerous to permit similar generalizations. The solvent of choice will probably be similar to the solvent used for succinoylations, but the nature of the anhydride and its reactivity will

have to be taken into account. From the available information regarding the condensation with maleic anhydride it would appear that tetrachloroethane is the most suitable solvent for the reaction with alkylated benzene derivatives.¹⁷¹ The claim in the patent literature that nitrobenzene is a good solvent for the reaction between maleic anhydride and polynuclear hydrocarbons could not be substantiated.³² The three cresol methyl ethers, veratrole, and hydroquinone dimethyl ether have been condensed with maleic anhydride in very good yield in nitrobenzene solution. The yields in carbon disulfide were generally lower.¹⁷⁶

The reaction time and reaction temperature will usually depend on the solvent employed and the compound to be substituted. Reactions in carbon disulfide are slow. However, the conveniently low boiling point of carbon disulfide makes it the solvent of choice where heating is required. It is necessary to heat reactions with the halobenzenes for twenty-four hours or more. Benzene is also used in conjunction with heating; it acts more vigorously because of its higher boiling point. Refluxing for one hour is usually sufficient with the alicyclic-aromatic compounds and diphenyl ether.

Of the two solvents that dissolve aluminum chloride, tetrachloroethane and nitrobenzene, the former gives the faster reaction. When employed for the succinylation of alkylbenzenes, a one- or two-hour standing period at room temperature is usually sufficient. In reactions of polynuclear hydrocarbons and their ethers a low reaction temperature has to be maintained while the reagents are slowly mixed. Reactions in nitrobenzene are generally slow, and this fact, combined with the low temperature at which reaction has to be carried out, require prolonged standing. The usual procedure is to add the reagents slowly at ice-bath temperature or below and after a few hours at that temperature to let the reaction mixture come to room temperature by allowing the ice to melt. A total period of twenty-four hours' standing after mixing the reagents is usually sufficient, but in some reactions a period of several days results in a higher yield. The reaction between 1-methyl-2-methoxynaphthalene and succinic anhydride results in a 41% yield after forty hours, a 63% yield after three days, and a 78% yield after five days.⁸⁴ In the succinylation of phenolic ethers using the tetrachloroethane-nitrobenzene mixture, three days' standing in the ice chest is recommended. With veratrole a 67% yield is secured when the low temperature is maintained for three days, but only 43% when the mixture is allowed to stand at room temperature for the same period of time.⁷¹ Anisole need not be cooled during the long standing time.²¹ When benzene is used as reactant and diluent, a short heating time

²¹ Fieser and Desreux, *J. Am. Chem. Soc.*, 60, 2255 (1938).

is usually necessary to compensate for the relative inertness of benzene.²⁰²

The order of addition of the reagents is not too important if the reaction is slow and the compound not sensitive to aluminum chloride. In all other cases, probably the majority, it is essential not to add the aluminum chloride alone to the compound to be substituted. It does not seem very important, however, whether the compound is added to the catalyst or vice versa. Haworth and collaborators conducted the reactions by adding slowly a mixture of the anhydride and the aromatic compound to the solution of aluminum chloride in nitrobenzene. Fieser and collaborators added the aluminum chloride through an addition tube to the solution of the other reagents. In some reactions the aluminum chloride can be dissolved in nitrobenzene and then added to the other reagents. One should also bear in mind that two moles of aluminum chloride is required for one mole of anhydride.^{12,13,196} In the older literature, and also in some recent work, this ratio was not used. An excess of aluminum chloride does not seem necessary; in a few reactions higher yields are reported when more catalyst is used, in others the yields are lower. The relative ratio of succinic anhydride-aluminum chloride and the compound to be substituted depends on the compounds; when the reactant is used as solvent it will obviously be present in excess. Often reagents can be used in equivalent amounts. An excess of about 20% of succinic anhydride-aluminum chloride with regard to other reactants generally results in a higher yield than an excess of the latter.²³

Apparatus and Isolation of Products

When the reaction does not require stirring, as is often the case when carbon disulfide or benzene is used as the solvent, an ordinary round-bottomed flask equipped with reflux condenser, calcium chloride tube, and gas-outlet tube is satisfactory. However, stirring is usually preferable even in a single-phase reaction because it provides faster mixing of the reagents and helps to eliminate the hydrogen chloride formed. A three-necked flask, equipped with a mercury-sealed stirrer, addition tube²⁰³ (or dropping funnel), thermometer, and a gas-outlet tube, is the most suitable apparatus. When the reaction is allowed to stand for a longer period of time, stirring is usually discontinued a few hours after mixing the reagents.

²⁰² Too long standing may promote side reactions, and the continuous evolution of hydrogen chloride is not always a sign that the reaction is still progressing in the desired direction. See ref. 195.

²⁰³ Fieser, *Experiments in Organic Chemistry*, 2nd ed., p. 311, D. C. Heath and Co. Boston, 1941.

The reaction mixture can be decomposed by the addition of ice and hydrochloric acid; but, as in all Friedel and Crafts reactions, it is better to pour the reaction mixture on ice and dilute hydrochloric acid in order to avoid local overheating or accumulation of too much hydrochloric acid.^{196a} If the decomposition is to be followed by steam distillation, it is advisable to carry out the decomposition of the reaction complex in a large round-bottomed flask which can be used directly for the steam distillation.

Carbon disulfide and benzene possess the advantage that they can easily be removed from the reaction mixture. The reaction complex usually precipitates during the reaction when carbon disulfide is the solvent, and the carbon disulfide layer, containing the unreacted reagents, can be decanted before decomposition; the remaining solvent is removed on the steam bath after acidification. The usual procedure with the other solvents is to remove them by steam distillation and to dissolve the remaining product in sodium carbonate solution. This is an important step, because alumina is always left behind with the acid and stays with the neutral materials when the acid is extracted with carbonate. Sodium hydroxide is obviously not suitable for this purpose because it dissolves alumina.

Nitrobenzene is not very volatile with steam, and even with an efficient steam-distillation apparatus a few hours are required to remove it completely.^{119,*} Small amounts of residual nitrobenzene tend to contaminate the final product and often cause it to separate as an oil after precipitation from the alkaline solution. It is good practice to filter the acid after the first steam distillation, or to decant the supernatant liquid if the acid is oily, return the acid to the original flask, add a solution of sodium carbonate, and continue the steam distillation.¹¹⁹ The second distillation, which must be begun carefully to avoid frothing, removes the last traces of solvents while the acid goes into solution as its sodium salt, leaving only the alumina and neutral products undissolved. The acid does not dissolve easily in carbonate solution because it is occluded by alumina, and, if the second steam distillation is omitted, prolonged boiling is often necessary to dissolve all the acidic material.²⁰⁴ The sodium carbonate solution is treated with charcoal while still warm and filtered, preferably with the help of some filtering aid, without which the alkaline solution filters very slowly owing to the suspended alumina. The solution should be placed in a large beaker, to prevent

* Holmes and Trevo, *Can. J. Research*, **22**, 109 (1944), found that some demethylation of 3,4-dimethoxybenzoylpropionic acid took place during steam distillation. Demethylation could be suppressed by separating the organic from the aqueous-acidic layer before the steam distillation.

²⁰⁴ Somerville and Allen, *Org. Syntheses, Coll. Vol. 2*, 81 (1943).

loss during acidification, and should be cooled before adding dilute acid. Since almost all the acids are very slightly soluble in cold water, ice can be added to the solution. If the first crop of material precipitates as an oil it can be disregarded or worked up separately, but usually the acids solidify readily in the cold.

In place of the second steam distillation, the reaction mixture can be dissolved in ether and the acid extracted with carbonate, or the filtered alkaline solution can be extracted with ether to remove the remaining solvent. But if much solvent is still present the separation of the layers is often tedious. Some acids form difficultly soluble sodium salts;^{29, 42-47, 114, 119} whenever this occurs isolation and crystallization of the sodium salt is the preferred method of purification.

EXPERIMENTAL PROCEDURES

Preparation of Anhydrides. Succinic anhydride is commercially available. It can be prepared from succinic acid by procedures described in *Organic Syntheses*.²⁰⁴

Glutaric anhydride can be prepared from glutaric acid by the methods just mentioned for succinic anhydride. Because of the low melting point of glutaric anhydride it is advisable to purify the product by vacuum distillation rather than crystallization.²⁰⁵

Methylsuccinic anhydride can be prepared by catalytic hydrogenation of citraconic anhydride.²⁰⁶ The synthesis of citraconic anhydride from citric acid is described in *Organic Syntheses*.²⁰⁷ A more convenient method for the preparation of methylsuccinic acid from ethyl crotonate has been described.²⁰⁸

dl- α,β -Dimethylsuccinic anhydride can be prepared from ethyl cyanoacetate and ethyl α -bromopropionate.^{119, 209}

Phenylsuccinic anhydride is prepared by dehydration of phenylsuccinic acid,^{114, 210} which is obtained from α -cyano- β -phenylacrylic acid.²¹¹

as-Dimethylsuccinic anhydride, *as*-methylethylsuccinic anhydride, and trimethylsuccinic anhydride can be synthesized by the method of Higson and Thorpe.²¹²

Maleic anhydride is available commercially.

²⁰⁴ *Org. Syntheses, Coll. Vol. 2*, 500 (1943).

²⁰⁵ Bergmann and Blum-Bergmann, *J. Am. Chem. Soc.*, **59**, 1573 (1937).

²⁰⁶ *Org. Syntheses, Coll. Vol. 2*, 368, 140 (1943).

²⁰⁷ *Org. Syntheses*, **26**, 54 (1946).

²⁰⁸ Bone and Sprankling, *J. Chem. Soc.*, **75**, 839 (1939).

²⁰⁹ *Org. Syntheses, Coll. Vol. 1*, 451 (1941).

²¹⁰ *Org. Syntheses, Coll. Vol. 1*, 181 (1941).

²¹¹ Higson and Thorpe, *J. Chem. Soc.*, **69**, 1455 (1906).

Polymeric anhydrides of higher dibasic acids can be prepared according to the directions on p. 263.

Preparation of β -Benzoylpropionic Acid. Detailed directions for this preparation, which illustrates the use of excess hydrocarbon as solvent, are given in *Organic Syntheses*.²²⁴

Preparation of β -(3-Acenaphthoyl)propionic Acid. Detailed directions are given in *Organic Syntheses*.^{113,225} "The procedure is a general one and may be used for the condensation of succinic anhydride with naphthalene and with the mono- and di-methylnaphthalenes, although in no other case are the purification and separation of isomers so easily accomplished."¹¹³ This general method can also be employed for the succinylation of higher polynuclear hydrocarbons.

Preparation of β -(*p*-Methoxybenzoyl)propionic Acid.⁷¹ A solution of 43 g. (0.4 mole) of anisole and 42 g. (0.42 mole) of succinic anhydride in 400 ml. of tetrachloroethane and 100 ml. of nitrobenzene is stirred and cooled to 0-5° (thermometer in liquid), and 112 g. (0.84 mole) of aluminum chloride is added gradually, the temperature being kept at 0-5°. At the end of the addition (one to two hours) a clear solution is usually obtained. It is allowed to stand at 0-5° (packed in ice in the cold room) for three days, during which time a complex sometimes separates.²²⁶ After ice and hydrochloric acid have been added and the solvents removed with steam, the product is either allowed to crystallize directly or it is dissolved in soda solution, and the solution is clarified with Norit and acidified. β -(*p*-Methoxybenzoyl)propionic acid is obtained as colorless needles, m.p. 146-147; 71 g. (85%).²²⁵

This is a general procedure for the succinylation of ethers of mono- and di-hydric phenols and naphthols, and it illustrates the use of a mixture of tetrachloroethane and nitrobenzene as a solvent.

Preparation of β -(*p*-Phenoxybenzoyl)propionic Acid.^{227,228} To a solution of 170 g. (1.0 mole) of diphenyl ether in 500 ml. of dry, thiophene-free benzene, 100 g. (1.0 mole) of finely ground succinic anhydride is added. Two moles of aluminum chloride (266.6 g.) is added all at once, and, after the initial reaction has ceased, the mixture is refluxed on the steam bath for one hour. The reaction mixture is decomposed with ice and hydrochloric acid, and the solvent is removed with steam. The

²²² Anhydrous hydrogen fluoride has also been employed as a condensing agent in the succinylation of acenaphthene. The yield is lower (49% of crude material), but the proportion of the two isomeric acids is approximately the same. Naphthalene does not react when hydrogen fluoride is used as the catalyst. Fieser and Herberg, *J. Am. Chem. Soc.*, 61, 1272 (1939).

²²⁴ It is reported that the low temperature during the three days' standing is not required for the preparation of β -(*p*-methoxybenzoyl)propionic acid. See ref. 201.

²²⁵ By the same procedure yields of 95% have been reported subsequently. Refs. 35, 198, 199.

crude acid is dissolved in sodium carbonate solution, the solution is filtered from aluminum oxide, and the filtrate is acidified. The yield of acid melting at 118–119° is 262–270 g. (97–100%).

Preparation of β -(*p*-Chlorobenzoyl)propionic Acid.²⁵ Fifty grams of chlorobenzene (0.44 mole) is dissolved in 200 ml. of carbon disulfide. Forty grams of succinic anhydride (0.4 mole) is added, followed by 110 g. of aluminum chloride (0.83 mole), and the mixture is refluxed on a water bath for twenty-four hours. The almost colorless carbon disulfide layer is then decanted, and the residue is treated with ice and hydrochloric acid. Any remaining solvent is removed by heating the mixture on the steam bath for a brief period. The crude acid is filtered, dissolved in soda solution, and clarified with charcoal. The yield of cream-colored acid, m.p. 132–133°, obtained on acidification is 34–42.5 g. (40–50%).²¹⁸

The other halogenated β -benzoylpropionic acids can be prepared by similar methods.

Condensation of Alkylbenzenes with Succinic Anhydride.²⁵ Sixty grams of finely powdered aluminum chloride is slowly added to 20 g. of succinic anhydride (0.2 mole), 0.22 mole of the hydrocarbon, and 75 ml. of tetrachloroethane. Most reactions (*p*-xylene is an exception) are complete in two or three hours. The products are worked up as usual and, after being precipitated from soda solution, are sufficiently pure for most purposes. The yields range from 80% to 90%.

Preparation of γ -(*p*-Methoxybenzoyl)butyric Acid.²⁵ A mixture of 25 ml. (0.23 mole) of anisole, 50 ml. of nitrobenzene, and 25 ml. of tetrachloroethane is cooled in a three-necked flask equipped with stirrer, dropping funnel, and gas-outlet tube. Aluminum chloride (57 g., 0.43 mole) is added, and the solution is cooled to 0–5°. A solution of 23 g. (0.2 mole) of glutaric anhydride in 25 ml. of tetrachloroethane is added through the dropping funnel over a period of forty-five minutes. After twenty-four hours, during which time the mixture is allowed to come to room temperature, the reaction is worked up in the usual way. The acid, once crystallized from ethanol, melts at 139.5–140.5° and weighs 38 g. (85%).

Preparation of α -Benzoylvaleric Acid.¹⁶¹ One hundred and forty-six grams (1.0 mole) of adipic acid is refluxed with 400 ml. of acetic anhydride for six hours. The excess acetic anhydride and the acetic acid formed are removed by distillation in vacuum up to 120° (bath temperature). The resulting polyanhydride is dissolved in 400 ml. of warm, dry benzene, and this solution is added with stirring over a period of one

²¹⁸ This acid can also be prepared with excess chlorobenzene as the solvent. Refs. 65, 66, 67.

hour to 300 g. (2.25 moles) of aluminum chloride suspended in 1.5 l. of dry benzene contained in a three-necked 3-l. flask fitted with a reflux condenser and a mechanical stirrer.

The reaction mixture, after having been allowed to stand overnight, is decomposed with ice, and 250 ml. of concentrated hydrochloric acid is added. The benzene layer is separated and extracted with dilute aqueous sodium hydroxide. The alkaline solution is acidified, and the crystalline precipitate of α -benzoylvaleric acid is filtered. The crude acid weighs 78 g. (75%). The product after crystallization from a benzene-petroleum ether mixture melts at 70–71°.

The extracted benzene is concentrated to a small volume and chilled; 56.5 g. (85%) of 1,4-dibenzoylbutane is obtained. The diketone after a single recrystallization from ethanol has a slightly pink color and melts at 105–106°.

TABULAR SURVEY OF FRIEDEL-CRAFTS REACTIONS WITH ALIPHATIC DIBASIC ACID ANHYDRIDES

In Tables VI–XV are summarized the reactions of the anhydrides of aliphatic dibasic acids with aromatic compounds reported prior to September 15, 1947. A few references available during 1948 have also been included. Some of the yields, particularly those recorded in the older literature, do not constitute the maximum yield but might be improved by choosing the right solvent and the right amount of catalyst. Whenever percentage yields are reported in the original paper they are quoted directly; all other yields have been computed from the available data and are based on the amount of anhydride. A dash indicates that the yield was not reported.

TABLE VI

REACTIONS OF SUCCINIC ANHYDRIDE WITH AROMATIC HYDROCARBONS AND HALOGEN DERIVATIVES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Reference * |
|-------------------|---|--|---------------------|---------------------------|
| Benzene | Benzoyl | Benzene | 6-7 | 1 |
| Benzene | Benzoyl | Benzene | 35 | 3 |
| Benzene | Benzoyl | Benzene | — | 2, 7, 217 |
| Benzene | Benzoyl | Benzene | 75 | 173 |
| Benzene | Benzoyl | Benzene | 39 | 218 |
| Benzene | Benzoyl | Benzene | 56 | 65 |
| Benzene | Benzoyl | Benzene | 77-82 | 204 |
| Benzene | Benzoyl | Benzene | 92-95 | 219 |
| Benzene | Benzoyl | CS ₂ | — | 32 |
| Fluorobenzene | 4-Fluorobenzoyl | CS ₂ | 27-33 | 35 |
| Chlorobenzene | 4-Chlorobenzoyl | Chlorobenzene | 47 | 65 |
| Chlorobenzene | 4-Chlorobenzoyl | CS ₂ | 40-50 | 38 |
| Bromobenzene | 4-Bromobenzoyl | Bromobenzene † | 74 | 65, 279 |
| Bromobenzene | 4-Bromobenzoyl | Bromobenzene | 27.5 | 67 |
| Bromobenzene | 4-Bromobenzoyl | CS ₂ | 30-40; 55 | 36 |
| Iodobenzene | 4-Iodobenzoyl | CS ₂ | 15-20 | 36 |
| Iodobenzene | Mixture of benzoyl and 4-iodobenzoyl | Iodobenzene | 13 | 283 |
| Toluene | 4-Toluyyl | Toluene | — | 7, 81, 217, 220, 221, 279 |
| Toluene | 4-Toluyyl | Toluene | 47; 71 | 222 |
| Toluene | 4-Toluyyl | Toluene | 94.5 | 223 |
| Toluene | 4-Toluyyl | CS ₂ | — | 32 |
| Toluene | 4-Toluyyl | CHCl ₃ :CHCl ₃ | 80-90 | 33 |
| Toluene | 4-Toluyyl | C ₆ H ₅ NO ₂ | 90 | 279a |
| o-Chlorotoluene | 4-Chloro-3-methylbenzoyl | CS ₂ | 60 | 35 |
| Ethylbenzene | 4-Ethylbenzoyl | CS ₂ | 68 | 35 |
| Ethylbenzene | 4-Ethylbenzoyl | Benzene | 57 | 7 |
| Ethylbenzene | 4-Ethylbenzoyl | Benzene | 80 | 34 |
| Ethylbenzene | 4-Ethylbenzoyl | CHCl ₃ :CHCl ₃ | 80 | 36 |
| Ethylbenzene | 4-Ethylbenzoyl | CHCl ₃ :CHCl ₃ | 80 | 200 |
| Ethylbenzene | 4-Ethylbenzoyl | + C ₆ H ₅ NO ₂ | — | — |
| o-Xylene | 3,4-Dimethylbenzoyl | Ethylbenzene | 57 | 224 |
| o-Xylene | 3,4-Dimethylbenzoyl | CS ₂ | — | 32 |
| o-Xylene | 3,4-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | 80-90 | 33 |
| o-Xylene | 3,4-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | 88 | 225 |
| o-Xylene | 3,4-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | 92.7 and 95.7 | 36 |
| m-Xylene | 2,4-Dimethylbenzoyl | CS ₂ | — | 32 |
| m-Xylene | 2,4-Dimethylbenzoyl | Benzene | — | 7 |
| m-Xylene | 2,4-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | 80-90 | 33 |
| m-Xylene | 2,4-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | Almost quantitative | 36 |
| m-Xylene | 2,4-Dimethylbenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 284 |
| p-Xylene | 2,5-Dimethylbenzoyl | CS ₂ | — | 32, 81 |
| p-Xylene | 2,5-Dimethylbenzoyl | CHCl ₃ :CHCl ₃ | 80-90 | 33, 36 |
| Mesitylene | 2,4,6-Triethylbenzoyl | CS ₂ | — | 32, 226 |

* References 217-296 appear on pps. 248-249.

† Nitrobenzene is not a satisfactory solvent in this reaction.

TABLE VI—Continued

REACTIONS OF SUCCINIC ANHYDRIDE WITH AROMATIC HYDROCARBONS AND HALOGEN DERIVATIVES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Reference * |
|------------------------|---|--|------------|-------------|
| Mesitylene (Continued) | 2,4,6-Trimethylbenzoyl | Mesitylene(?) | — | 27 |
| Mesitylene | 2,4,6-Trimethylbenzoyl | $\text{CHCl}_3\text{-CHCl}_3$ | 91 | 26 |
| 1,3,4-Trimethylbenzene | 2,4,5-Trimethylbenzoyl | CS_2 | — | 32 |
| n-Propylbenzene | 4-n-Propylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 63 | 37c |
| Isopropylbenzene | 4-Isopropylbenzoyl | CS_2 | — | 32 |
| Isopropylbenzene | 4-Isopropylbenzoyl | $\text{CHCl}_3\text{-CHCl}_3$ | 80-90 | 33 |
| Isopropylbenzene | 4-Isopropylbenzoyl | $\text{CHCl}_3\text{-CHCl}_3$ + | 58 | 26 |
| Isopropylbenzene | 4-Isopropylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 59 | 37a |
| p-Ethyltoluene | 4-Methyl-3-ethylbenzoyl or 4-ethyl-3-methylbenzoyl | CS_2 | — | 32 |
| Durene | 2,3,5,6-Tetramethylbenzoyl | CS_2 | — | 32 |
| p-Cymene | 2-Methyl-5-isopropylbenzoyl | CS_2 | — | 32 |
| p-Cymene | 2-Methyl-5-isopropylbenzoyl | CS_2 , benzene, or $\text{CHCl}_3\text{-CHCl}_3$ | Low † | 36 |
| p-Cymene | 2-Methyl-5-isopropylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 70 | 255 |
| tert-Butylbenzene | 4-tert-Butylbenzoyl | CS_2 | 55 | 35 |
| tert-Butylbenzene | 4-tert-Butylbenzoyl | CS_2 | — | 26, 228 |
| sec-Amylbenzene | sec-Amylbenzoyl | sec-Amylbenzene | — | 272 |
| tert-Amylbenzene | 4-tert-Amylbenzoyl | CS_2 | 50 | 36 |
| Pentamethylbenzene | Pentamethylbenzoyl | CS_2 | — | 32 |
| sec-Octyltoluene | sec-Octyltolyl | sec-Octyltoluene | — | 272 |
| Di-tert-butylbenzene | 4-tert-Butylbenzoyl and an unidentified acid | CS_2 | — | 31 |
| Hydrindene | 5-Hydrindoyl | $\text{CHCl}_3\text{-CHCl}_3$ + $\text{C}_6\text{H}_5\text{NO}_2$ | 97 | 55 |
| Hydrindene | 5-Hydrindoyl | $\text{CHCl}_3\text{-CHCl}_3$ + $\text{C}_6\text{H}_5\text{NO}_2$ | 60 | 56 |
| Hydrindene | 5-Hydrindoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 42 | 56, 229 |
| Hydrindene | 5-Hydrindoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 37 | 57 |
| Hydrindene | 5-Hydrindoyl | Benzene | 62, 79 ‡ | 59 |
| Tetralin | 2-Tetroyl | Benzene | 52 | 7 |
| Tetralin | 2-Tetroyl | Benzene | 76; 72.5 | 59, 56 |
| Tetralin | 2-Tetroyl | Benzene | Good yield | 250 |
| Tetralin | 2-Tetroyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 70 | 231 |
| Naphthalene | Mixture of 1- and 2-naphthoyl † | CS_2 | — | 222 |

* References 217-256 appear on pp. 255-259.

† The product of all runs was of poor quality, possibly because of isomer present in commercial p-cymene. The best product was obtained when the reaction was run in a mixture of tetrachloroethane and nitrobenzene.

‡ The yield refers to a crude product; benzene is not a suitable solvent for the succinylation of hydrindene.

§ Heat increased the proportion of the 2-isomer.

TABLE VI—Continued

REACTIONS OF SUCCINIC ANHYDRIDE WITH AROMATIC HYDROCARBONS AND HALOGEN DERIVATIVES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Reference * |
|---------------------------------|---|--|------------|-------------|
| Naphthalena (Continued) | Mixture of 1- and 2-naphthoyl | Benzene | — | 7 |
| Naphthalena | Mainly 2-naphthoyl | CS_2 | 6.8-7.8 | 233 |
| Naphthalena | Mixture of 1- and 2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 91 | 40, 238 |
| Naphthalena | Mixture of 1- and 2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 234, 238 |
| Naphthalena | 1-Naphthoyl and 2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 33 29 | 6 |
| Naphthalena | 1-Naphthoyl and 2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 36 47 | 39 |
| 1-Methylnaphthalena | 1-Methyl-4-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 80 | 68 |
| 2-Methylnaphthalena | 2-Methyl-6-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 79 | 112 |
| 2-Methylnaphthalena | 2-Methyl-6-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 60-75 | 39 |
| 2-Methylnaphthalena | 6-Methyl-2-naphthoyl and 6-methyl-1-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 50 38 | 114 |
| 1-Ethyl naphthalena | 4-Ethyl-1-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 74 | 40 |
| 2-Ethyl naphthalena | 6-Ethyl-2-naphthoyl | $\text{CHCl}_3/\text{CHCl}_3$ | 66 | 113 |
| 2,3-Dimethyl naphthalena | 6,7-Dimethyl-1-2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 70 | 115, 215 |
| 2,7-Dimethyl naphthalena | 2,7-Dimethyl-1-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 60-75 | 39 |
| 2-Isopropyl naphthalena | 6-Isopropyl-2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 28 | 112 |
| 2-n-Propyl naphthalena | 6-n-Propyl-2-naphthoyl(?) | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 37, 112 |
| 2-tert-Butyl naphthalena | 6-tert-Butyl-2-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 37 | 35 |
| 1,2,3,4-Tetramethyl-naphthalena | 1,2,3,4-Tetramethyl-6-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 90 | 236 |
| Phenylcyclohexana | 4-Cyclohexylbenzoyl | $\text{CHCl}_3/\text{CHCl}_3 + \text{C}_6\text{H}_5\text{NO}_2$ | 83 | 38 |
| Phenylcyclohexana | 4-Cyclohexylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 64 |
| Diphenyl | 4-Phenylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 90; 83 | 62, 36 |
| Biphenyl | 4-Phenylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 70 | 63 |
| Acenaphthene | 3-Acenaphthoyl and 1-acenaphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 78† 15 | 39 |
| Acenaphthene | 3-Acenaphthoyl and 1-acenaphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 81 5 | 119 |
| Acenaphthene | Mixture of 1- and 3-acenaphthoyl | Benzene | Poor | 30 |
| Diphenylmethane | 4-Benzylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 59 |
| Diphenylmethane | 4-Benzylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 53.4 | 36 |
| Fluorene | 2-Fluoroyl | Benzene | 75-80 | 58, 36 |
| Fluorene | 2-Fluoroyl | $\text{C}_6\text{H}_5\text{NO}_2$ or $\text{CHCl}_3/\text{CHCl}_3$ | 80 | 241 |
| Cyclohexane-1-epi-hydrindene | 5-(or 6)-Cyclohexane-1-epi-hydrindoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 242 |
| 9,10-Dihydroanthracene | 9-(9,10-Dihydroanthroyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 35 | 59 |
| 9,10-Dihydroanthracene | 2-Anthroyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 11 | 21 |
| Anthracene | 2-Anthroyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 22 | 30, 21 |
| Anthracene | 2-Anthroyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 15 | 43 |

* References 217-236 appear on pp. 283-289.

† These are the yields when the reaction is conducted at 0°; at -15° the yields are 8% and 5% respectively.

TABLE VI—*Continued*

REACTIONS OF SUCCINIC ANHYDRIDE WITH AROMATIC HYDROCARBONS AND HALOGEN DERIVATIVES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|---|--|--------------|------------|------------------|
| Anthracene (<i>Continued</i>) | 1-Anthroyl and 2-anthroyl | $C_6H_5NO_2$ | — | 44 |
| Anthracene | 9-(9,10-Dihydro)anthroyl | Benzene | — | 30 |
| 9,10-Dihydrophenanthrene | 2-(9,10-Dihydrophen- anthroyl) | $C_6H_5NO_2$ | 98 | 109 |
| 9,10-Dihydrophenanthrene | 2-(9,10-Dihydrophen- anthroyl) | $C_6H_5NO_2$ | 96 | 110, 237 |
| 1,2,3,4-Tetrahydrophen- anthrene | 9-(1,2,3,4-Tetrahydro- phenanthroyl) and 7-(1,2,3,4-tetrahydro- phenanthroyl) | $C_6H_5NO_2$ | 78 5 | 40, 106, 36 |
| 1,2,3,4,5,6,7,8-Octahydro- phenanthrene | 9-(1,2,3,4,5,6,7,8-Octa- hydrophenanthroyl) | CS_2 | 86 | 108 |
| 1,2,3,4,9,10,11,12-Octa- hydrophenanthrene | 6-(1,2,3,4,9,10,11,12-Octa- hydrophenanthroyl) | $C_6H_5NO_2$ | 31 | 107 |
| Phenanthrene | 3-Phenanthroyl (and an isomer) | $C_6H_5NO_2$ | 60 | 41 |
| Phenanthrene | 3-Phenanthroyl and 2-phenanthroyl | $C_6H_5NO_2$ | 60(?) 5 | 42 |
| 4,5-Methylene-9,10-di- hydrophenanthrene | 4,5-Methylene-9,10-di- hydro-2-phenanthroyl | $C_6H_5NO_2$ | 99 | 54 |
| 4,5-Methylenephenanthrene | 4,5-Methylene-1-phenan- throyl | $C_6H_5NO_2$ | 45.4 | 54 |
| 4-Methyl-1,2,3,4-tetrahy- drophenanthrene | 4-Methyl-1,2,3,4-tetrahy- dro-9-phenanthroyl † | $C_6H_5NO_2$ | — | 286 |
| 9-Methyl-1,2,3,4-tetrahy- drophenanthrene | 9-Methyl-1,2,3,4-tetrahy- dro-7-phenanthroyl | $C_6H_5NO_2$ | 62 | 113 |
| 3-Methylphenanthrene | 6-(3-Methylphenanthroyl) | $C_6H_5NO_2$ | 36.5 | 53 |
| 4-Methylphenanthrene | 3-(5-Methylphenanthroyl) and some 1-(4-methyl- phenanthroyl) | $C_6H_5NO_2$ | 22 | 52 |
| 9,10-Dihydroretene | 9,10-Dihydro-2-retoyl | $C_6H_5NO_2$ | 80 | 49 |
| Retene | 3-Retoyl | Benzene | 58.5 | 48 |
| Retene | 3-Retoyl | $C_6H_5NO_2$ | 21 | 49 |
| 1,2,3,4-Tetrahydro-8,9- acephenanthrene | 5-(1,2,3,4-Tetrahydro-8,9- acephenanthroyl) | $C_6H_5NO_2$ | 83 | 61 |
| 1,2,3,6,7,8-Hexahydro- pyrene | 1,2,3,6,7,8-Hexahydro-4- pyrenoyl | $C_6H_5NO_2$ | 67.5 | 45 |
| Pyrene | 1-Pyrenoyl | $C_6H_5NO_2$ | 62 | 45 |
| Pyrene | 1-Pyrenoyl | $C_6H_5NO_2$ | 90-94 | 46 |
| Pyrene | 1-Pyrenoyl | $C_6H_5NO_2$ | 96 | 47 |
| Pyrene | 1-Pyrenoyl | $C_6H_5NO_2$ | 90 | 239 |
| Chrysene | 2-Chrysenoyl | Benzene | 50-55 | 50, 240 |
| Chrysene | 4- or 5-Chrysenoyl ‡ | $C_6H_5NO_2$ | 37 § | 50 |
| Chrysene | 4- or 5-Chrysenoyl and some of the 2-isomer | $C_6H_5NO_2$ | 5.5, 9.1 ¶ | 51 |

* References 217-296 appear on pp. 288-289.

† No analysis was reported for this product.

‡ The author assumed this to be the 1-acid, but see ref. 51.

§ This yield refers to a crude product.

¶ This experiment was run at 30°; at 0° an inseparable mixture of acids was obtained.

TABLE VII

REACTIONS OF SUCCINIC ANHYDRIDE WITH PHENOLIC ETHERS

| Ether | Product β -Arylpropionic Acid | Solvent | Yield % | Refer- ence * |
|---|---|--|------------------------|------------------|
| Anisole | 4-Anisoyl | Anisole | 43-55 | 69 |
| Anisole | 4-Anisoyl | CS ₂ | — | 26, 70 |
| Anisole | 4-Anisoyl | CS ₂ | 65 | 175 |
| Anisole | 4-Anisoyl | Benzene | — | 7 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₂ | 80.5 | 23 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₃ | Almost quantitative | 243 |
| Anisole | 4-Anisoyl | C ₆ H ₅ NO ₂ | Almost quantitative | 244 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₂ + C ₆ H ₅ NO ₂ | 85 | 71 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₂ + C ₆ H ₅ NO ₂ | 90 | 201 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₂ + C ₆ H ₅ NO ₂ | 93.5 | 86 |
| Anisole | 4-Anisoyl | CHCl ₂ CHCl ₂ + C ₆ H ₅ NO ₂ | 95 | 198, 199 |
| Anisole | 4-Anisoyl | C ₆ H ₅ NO ₂ † | 75-85 | 237 |
| Anisole | 4-Anisoyl | C ₆ H ₅ NO ₂ | 83 | 74, 274 |
| Anisole | 4-Anisoyl and 1,2-di-(p-tol) deoxybenzoyl ethane | C ₆ H ₅ NO ₂ | 34.5 9.6 | 75 |
| Anisole | 4-Anisoyl | CH ₃ CH ₂ CH ₂ NO ₂ | 86-90 | 259 |
| <i>o</i> -Chloroanisole | 4-Methoxy-3-chlorobenzoyl | ? | — | 80 |
| Phenetole | 4-Ethoxybenzoyl | Phenetole | 45-63 | 3 |
| Phenetole | 4-Ethoxybenzoyl | Phenetole | 69 | 72 |
| Phenetole | 4-Ethoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73, 274 |
| <i>o</i> -Chlorophenetole | 4-Ethoxy-3-chlorobenzoyl | ? | — | 80 |
| <i>n</i> -Propyl phenyl ether ‡ | 4- <i>n</i> -Propoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73, 274 |
| <i>n</i> -Butyl phenyl ether | 4- <i>n</i> -Butoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73, 274 |
| Isobutyl phenyl ether | 4-Isobutoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73 |
| Isamyl phenyl ether | 4-Isamyoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73 |
| <i>n</i> -Hexyl phenyl ether | 4- <i>n</i> -Hexoxybenzoyl | C ₆ H ₅ NO ₂ | 80-90 | 73 |
| β -Phenoxyethoxyethyl chloride | (β -Chloroethoxyethoxy)benzoyl | CS ₂ | — | 267 |
| <i>n</i> -Cresyl methyl ether | 4-Methoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 74 | 74 |
| <i>n</i> -Cresyl methyl ether | 4-Methoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | — | 75, 274 |
| <i>n</i> -Cresyl ethyl ether | 4-Ethoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 82 | 273 |
| <i>n</i> -Cresyl <i>n</i> -propyl ether | 4- <i>n</i> -Propoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 83 | 273 |
| <i>n</i> -Cresyl isopropyl ether | 4-Isopropoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 14 | 273 |
| <i>n</i> -Cresyl <i>n</i> -butyl ether | 4- <i>n</i> -Butoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 84 | 273 |
| <i>n</i> -Cresyl isobutyl ether | 4-Isobutoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 80 | 273 |
| <i>n</i> -Cresyl isamyl ether | 4-Isamyoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 85 | 273 |
| <i>n</i> -Cresyl <i>n</i> -hexyl ether | 4- <i>n</i> -Hexoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 65 | 273 |
| <i>n</i> -Cresyl <i>n</i> -heptyl ether | 4- <i>n</i> -Heptoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | 85 | 273 |
| <i>m</i> -Cresyl methyl ether | 4-Methoxy-3-methylbenzoyl | CS ₂ | — | 745 |
| <i>m</i> -Cresyl methyl ether | 4-Methoxy-3-methylbenzoyl | C ₆ H ₅ NO ₂ | — | 74, 75, 274 |

* References 217-296 are on pp. 255-289.

† In nitroethane the yield was slightly lower.

‡ Isopropyl phenyl ether did not react with succinic anhydride.

TABLE VII—Continued

REACTIONS OF SUCCINIC ANHYDRIDE WITH PHENOLIC ETHERS

| Ether | Product β -Aroylpropionic Acid | Solvent | Yield % | Reference * |
|---|--|------------------------------|---------------------|-------------|
| <i>m</i> -Cresyl methyl ether (Continued) | Mixture of equal amounts of 4-methoxy-2-methylbenzoyl and 4-ethoxy-2-methylbenzoyl | $C_6H_5NO_2$ | — | 151c |
| <i>m</i> -Cresyl ethyl ether | 4-Ethoxy-2-methylbenzoyl | $C_6H_5NO_2$ | 65 | 273 |
| <i>m</i> -Cresyl <i>n</i> -propyl ether † | 4- <i>n</i> -Propoxy-2-methylbenzoyl | $C_6H_5NO_2$ | 65 | 273 |
| <i>m</i> -Cresyl <i>n</i> -butyl ether | 4- <i>n</i> -Butoxy-2-methylbenzoyl | $C_6H_5NO_2$ | 50 | 273 |
| <i>m</i> -Cresyl isobutyl ether | 4-Isobutoxy-2-methylbenzoyl | $C_6H_5NO_2$ | 49 | 273 |
| <i>m</i> -Cresyl isomyl ether | 4-Isomyl-oxy-2-methylbenzoyl | $C_6H_5NO_2$ | 50 | 273 |
| <i>m</i> -Cresyl <i>n</i> -hexyl ether | 4- <i>n</i> -Hexyloxy-2-methylbenzoyl | $C_6H_5NO_2$ | 55 | 273 |
| <i>p</i> -Cresyl methyl ether | 2-Methoxy-5-methylbenzoyl | $C_6H_5NO_2$ | — | 74, 75, 274 |
| <i>p</i> -Cresyl ethyl ether | 2-Ethoxy-5-methylbenzoyl | $C_6H_5NO_2$ | 75 | 273 |
| <i>p</i> -Cresyl <i>n</i> -propyl ether † | 2- <i>n</i> -Propoxy-5-methylbenzoyl | $C_6H_5NO_2$ | 80 | 273 |
| <i>p</i> -Cresyl <i>n</i> -butyl ether | 2- <i>n</i> -Butoxy-5-methylbenzoyl | $C_6H_5NO_2$ | 75 | 273 |
| <i>p</i> -Cresyl isobutyl ether | 2-Isobutoxy-5-methylbenzoyl | $C_6H_5NO_2$ | 60 | 273 |
| <i>p</i> -Cresyl isomyl ether | 2-Isomyl-oxy-5-methylbenzoyl | $C_6H_5NO_2$ | 80 | 273 |
| <i>p</i> -Cresyl <i>n</i> -hexyl ether | 2- <i>n</i> -Hexyloxy-5-methylbenzoyl | $C_6H_5NO_2$ | 60 | 273 |
| 2,2-Dimethylanisole | 4-Methoxy-2,3-dimethylbenzoyl | Benzene | 50 | 78 |
| 2,4-Dimethylanisole | 2-Methoxy-3,5-dimethylbenzoyl | Benzene | 24.5 | 245 |
| 2,5-Dimethylanisole | 4-Methoxy-2,5-dimethylbenzoyl | Benzene | 75 | 247 |
| 2,5-Dimethylanisole | 4-Methoxy-2,5-dimethylbenzoyl | $CHCl_3:CHCl_2$ | 86 | 76 |
| 2,6-Dimethylanisole | 4-Methoxy-3,5-dimethylbenzoyl | $C_6H_5NO_2$ | 35 | 79 |
| 2-Methyl-5-ethylanisole | 4-Methoxy-3-methyl-5-ethylbenzoyl | $C_6H_5NO_2$ | 90 | 77 |
| 3-Methyl-5-ethylanisole | 4-Methoxy-2-methyl-5-ethylbenzoyl | $C_6H_5NO_2$ | Quantitative | 77 |
| 3-Methyl-6-isopropylanisole | 4-Methoxy-2-methyl-5-isopropylbenzoyl | $C_6H_5NO_2$ | — | 74 |
| 2-Methyl-6-isopropylanisole | 4-Methoxy-2-methyl-5-isopropylbenzoyl | $C_6H_5NO_2$ | 81.3 | 73 |
| 4- <i>tert</i> -Butylanisole | 2-Methoxy-5- <i>tert</i> -butylbenzoyl | $C_6H_5NO_2$ | Good | 245 |
| Vanillin | 3,4-Dimethoxybenzoyl | $C_6H_5NO_2$ | 85 | 145, 255 |
| Vanillin | 3,4-Dimethoxybenzoyl | $C_6H_5NO_2$ | 44 | 22, 275 |
| Vanillin | 3,4-Dimethoxybenzoyl | $C_6H_5NO_2$ | 93 | 249 |
| Vanillin | 2,4-Dimethoxybenzoyl | $C_6H_5NO_2$ | 73 | 71 |
| Vanillin | 3,4-Dimethoxybenzoyl | $C_6H_5NO_2$ | — | 250, 251 |
| Vanillin | 3,4-Dimethoxybenzoyl | CS_2 | — | 25, 251 |
| Vanillin | 3,4-Dimethoxybenzoyl | CS_2 | 45 | 22, 71 |
| Vanillin | 2,4-Dimethoxybenzoyl | $CHCl_3:CHCl_2$ | Nearly quantitative | 243 |
| Vanillin | 3,4-Dimethoxybenzoyl | $CHCl_3:CHCl_2$ | 64 | 22 |
| Vanillin | 2,4-Dimethoxybenzoyl | $CHCl_3:CHCl_2 + C_6H_5NO_2$ | 67 | 71 |
| Vanillin | 2,4-Dimethoxybenzoyl | $CHCl_3:CHCl_2 + C_6H_5NO_2$ | 84 | 252 |

* References 247-250 are on pp. 258-259.

† The isopropyl ether did not react with succinic anhydride.

TABLE VII—Continued

REACTIONS OF SUCCINIC ANHYDRIDE WITH PHENOLIC ETHERS

| Ether | Product <i>β</i> -Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|--|---|--|------------|------------------|
| Veratrola (Continued) | 3,4-Dimethoxybenzoyl and 2-methoxy-4-hydroxybenzoyl | $\text{CHCl}_3\text{CHCl}_3 + \text{C}_6\text{H}_5\text{NO}_2$ | 84, 8, 81 | 275, 206 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | Resorcinol dimethyl ether | — | 253 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | CS_2 | — | 23, 26 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | CS_2 | 65-75 † | 25 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | CS_2 | 50 | 22 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 60 | 22 |
| Resorcinol dimethyl ether | 3,4-Dimethoxybenzoyl, 3-hy- droxy-4-methoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 90 ‡ | 26 |
| Resorcinol dimethyl ether | 3-Hydroxy-4-methoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | — | 271 |
| Resorcinol dimethyl ether | 2,4-Dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 88 | 23 |
| Resorcinol dimethyl ether | 2-Hydroxy-4-methoxybenzoyl | Resorcinol dimethyl ether | — | 23 |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | CS_2 | 40, — | 22, 26 |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 45 | 22 |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 70 | 22, 274, 278 |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ + $\text{C}_6\text{H}_5\text{NO}_2$ | 81.9 | 80, 30 |
| Hydroquinone diethyl ether | 2,5-Diethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ + $\text{C}_6\text{H}_5\text{NO}_2$ | 88, 62 | 30 |
| Hydroquinone diethyl ether | 2,5-Diethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 52.5 | 36 |
| Oronol dimethyl ether | 2,4-Dimethoxy-6-methylbenzoyl | CS_2 | 40 | 27 |
| Oronol dimethyl ether | 2,4-Dimethoxy-6-methylbenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 45 | 27 |
| Oronol dimethyl ether | 2,4-Dimethoxy-6-methylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 60 | 27 |
| Hydroxyhydroquinone trimethyl ether | 2,4,6-Trimethoxybenzoyl | CS_2 | — | 26 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | CS_2 | — | 26 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | CS_2 | 50 | 27 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 57 | 23 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 60 | 27 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | — | 271 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | $\text{CHCl}_3\text{CHCl}_3$ | 31 | 78a |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 45 | 27 |
| Pyrogallol trimethyl ether | 2-Hydroxy-3,4-dimethoxybenzoyl and 2,3,4-trimethoxybenzoyl † | $\text{CHCl}_3\text{CHCl}_3 + \text{C}_6\text{H}_5\text{NO}_2$ | — | 23a |
| 1-Methoxy-5,6,7,8-tetrahydro- naphthalene | 5,6,7,8-Tetrahydro-4-methoxy- 1-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 6.8 82 | 254 |

* References 217-296 are on pp. 288-289

† The yield refers to the dimethoxy acid after methylation of the accompanying hydroxy acid. The yield of demethylated acid was as much as 23% in one run, but demethylation can be suppressed by separating the organic layer from the aqueous-acid layer before steam distillation.

‡ Some demethylation took place.

§ The reaction was carried out at 50-60°. The yield refers to the total product.

|| The reaction mixture was steam-distilled after the organic layer had been separated from the acidic aqueous layer. See also ref. 273.

TABLE VII—Continued

REACTIONS OF SUCCINIC ANHYDRIDE WITH PHENOLIC ETHERS

| Ether | Product β -Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|---|---|---------------------------------------|------------------------|------------------|
| 6-Ethoxy-1,2,3,4-tetrahydro- naphthalene | 1,2,3,4-Tetrahydro-6-ethoxy-7- naphthoyl and 1,2,3,4- tetrahydro-6-ethoxy-8- naphthoyl | $C_6H_5NO_2$ | — | 255 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | CS_2 | — | 81 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | CS_2 | 30-40 | 256 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | Petroleum ether | 40 | 256 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $CHCl_2CHCl_2$ | 98 | 71 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $CHCl_2CHCl_2$ | 92 | 256 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $C_6H_5NO_2$ | 92 | 256 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $C_6H_5NO_2$ | 83 | 82 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $C_6H_5NO_2$ | — | 86 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $C_6H_5NO_2$ † | — | 85, 86 |
| 2-Methoxynaphthalene | 2-Methoxy-1-naphthoyl | CS_2 | — | 84a |
| 2-Methoxynaphthalene | 2-Methoxy-8-naphthoyl | CS_2 | 33.5 crude | 39 |
| 2-Methoxynaphthalene | 2-Methoxy-6-naphthoyl | $C_6H_5NO_2$ | 60-75 | 83 |
| 2-Methoxynaphthalene | 2-Methoxy-6-naphthoyl | $C_6H_5NO_2$ | 33 ‡ | 86 |
| 2-Methoxynaphthalene | 2-Methoxy-6-naphthoyl | $C_6H_5NO_2$ | — | 85 |
| 2-Methoxynaphthalene | 2-Methoxy-6-naphthoyl and 2-methoxy-1-naphthoyl | $C_6H_5NO_2$ | 9 parts 1 part § | — |
| 2-Methoxynaphthalene | 2-Methoxy-1-naphthoyl | (?) | — | 274 |
| 1-Ethoxynaphthalene | 4-Ethoxy-1-naphthoyl | CS_2 | — | 257 |
| 1-Methoxy-7-methylnaphthalene | 1-Methoxy-7-methyl-4-naphthoyl | Benzene | — | 81 |
| 1-Methoxy-7-isopropylnaphthalene | 1-Methoxy-7-isopropyl-4-naph- thoyl | Benzene or, better, $CHCl_2CHCl_2$ | 90 | 258 |
| 1-Methyl-2-methoxynaphthalene | 1-Methyl-2-methoxy-6-naphthoyl | $C_6H_5NO_2$ | 78 ¶ | 84 |
| 2-Methoxy-6-methylnaphthalene | 2-Methoxy-6-methyl-1-naphthoyl | $C_6H_5NO_2$ | 40 | 116 |
| 1,5-Dimethoxynaphthalene | 4,8-Dimethoxy-1-naphthoyl | $CHCl_2CHCl_2$ + $C_6H_5NO_2$ | 93 ¶ | 87 |
| 1,5-Dimethoxynaphthalene | 4,8-Dimethoxy-1-naphthoyl | CS_2 | 21 | 24 |
| 1,5-Dimethoxynaphthalene | 4,8-Dimethoxy-1-naphthoyl | $C_6H_5NO_2$ | 85 | 24 |
| 1,5-Dimethoxynaphthalene | 4-Hydroxy-8-methoxy-1-naph- thoyl ** | $CHCl_2CHCl_2$ | 80 | 24 |
| 2,6-Dimethoxynaphthalene | 2,6-Dimethoxy-1-naphthoyl | $CHCl_2CHCl_2$ + $C_6H_5NO_2$ | 82 | 87 |
| Diphenyl ether | 4-Phenoxybenzoyl | CS_2 | 93 | 91 |
| Diphenyl ether | 4-Phenoxybenzoyl | CS_2 | 58 | 92 |
| Diphenyl ether | 4-Phenoxybenzoyl | Benzene | Almost quantitative | 36 |
| Diphenyl ether | 4-Phenoxybenzoyl | Benzene | 83 | 93 |
| Diphenyl ether | 4-Phenoxybenzoyl | $C_6H_5NO_2$ | — | 274 |
| Diphenyl sulfide | 4-Mercaptophenylbenzoyl | Benzene | 94 | 93a |
| 4-Methoxybiphenyl | 4-Methoxy-4'-xenylyl, 4-methoxy- 3-xenylyl | $C_6H_5NO_2$ | 24.5 60 | 105 |

* References 217-296 are on pp. 288-289.

† In carbon disulfide a small amount of 1-methoxy-4-dithiocarboxylic acid was obtained.

‡ A mixture was obtained and some of the acid was isolated as the ethyl ester.

§ The total yield of pure acids was 45%.

¶ This yield refers to a reaction time of five days; see p. 258.

¶ With three equivalents of aluminum chloride the yield was 98%.

** This was the reaction product when the reaction was conducted between 40° and 74°.

TABLE VIII

REACTIONS OF SUCCINIC ANHYDRIDE WITH PHENOLS

| Phenol | Product β-Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|------------------------------------|---|---|----------------|------------------|
| Phenol | 2-Hydroxybenzoyl | $\text{CHCl}_2\text{CHCl}_2$ | 62 | 28, 243 |
| Phenol | 2-Hydroxybenzoyl, 4-hydroxybenzoyl | $\text{CHCl}_2\text{CHCl}_2$ | 30-35 2-3 | 88, 278 |
| Phenol | 2-Hydroxybenzoyl, 4-hydroxybenzoyl | $\text{CHCl}_2\text{CHCl}_2$ | 20 3 | 89 |
| <i>o</i> -Cresol | 2-Hydroxy-3-tolyl, 4-hydroxy-3-tolyl | $\text{CHCl}_2\text{CHCl}_2$ | 35-40 15-20 | 88 |
| <i>m</i> -Cresol | 2-Hydroxy-4-tolyl, 4-hydroxy-3-tolyl | $\text{CHCl}_2\text{CHCl}_2$ | 60-65 1-2 | 88, 278 |
| <i>p</i> -Cresol | 2-Hydroxy-3-tolyl | $\text{CHCl}_2\text{CHCl}_2$ | 40-45 | 88 |
| Resorcinol | 2,4-Dihydroxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 40 | 90, 290 |
| Resorcinol | — | — | — | 281 |
| 3,5-Dihydroxytoluene | 2,6-Dihydroxy-4-methyl- benzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 8 | 90 |
| Hydroquinone | — | CS_2 , $\text{C}_6\text{H}_5\text{NO}_2$ $\text{CHCl}_2\text{CHCl}_2$ | — | 90 |
| Quinalol | — | CS_2 , $\text{C}_6\text{H}_5\text{NO}_2$ $\text{CHCl}_2\text{CHCl}_2$ | — | 22 |
| Quinalol | 3-Methoxy-4-hydroxybenzoyl | $\text{CHCl}_2\text{CHCl}_2$ + $\text{C}_6\text{H}_5\text{NO}_2$ | Low | 275 |
| Resorcinol monomethyl ether | 2-Hydroxy-4-methoxybenzoyl | CS_2 | 35 | 22, 280 |
| Resorcinol monomethyl ether | 2-Hydroxy-4-methoxybenzoyl | $\text{CHCl}_2\text{CHCl}_2$ | 40 | 22 |
| Resorcinol monomethyl ether | 2-Hydroxy-4-methoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 40 | 22 |
| Hydroquinone mono- methyl ether | — | CS_2 , $\text{CHCl}_2\text{CHCl}_2$, $\text{C}_6\text{H}_5\text{NO}_2$ | — | 22 |
| Orcinol monomethyl ether | 2-Methoxy-4-hydroxy-6- methylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 25 | 27 |
| Phloroglucinol | — | $\text{CHCl}_2\text{CHCl}_2$, $\text{C}_6\text{H}_5\text{NO}_2$ | — | 90 |
| 1-Naphthol | — | $\text{CHCl}_2\text{CHCl}_2$, $\text{C}_6\text{H}_5\text{NO}_2$ | — | 90 |

* References 217-290 are on pp. 258-289.

TABLE IX

REACTIONS OF SUCCINIC ANHYDRIDE WITH HETEROCYCLES AND MISCELLANEOUS COMPOUNDS

| Starting Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Refer- ences * |
|--------------------------------------|--|-----------------|------------|-------------------|
| Thiophene | 2-Thienoyl | $C_6H_5NO_2$ | 51; 58.5 | 94; 164 |
| Thiophene | 2-Thienoyl | CS_2 | 21 | 94 |
| 2,5-Dimethylthiophene | 2,5-Dimethyl-3-thienoyl | $C_6H_5NO_2$ | — | 95 |
| Benzothiophene (thionaphthene) | 3-Thionaphthoyl | $C_6H_5NO_2$ | 43 | 96 |
| Thiochromane | 6-Thiochromanoyl | $C_6H_5NO_2$ | 90 | 98 |
| Dibenzothiophene | 2-Dibenzothienoyl | $CHCl_2:CHCl_2$ | 66 | 97 |
| | | + | | |
| Dibenzothiophene | 2-Dibenzothienoyl | $C_6H_5NO_2$ | 61.5 | 96 |
| Diphenylene oxide | 2-Dibenzofuroyl | ? | — | 99 |
| Diphenylene oxide | 2-Dibenzofuroyl | $C_6H_5NO_2$ | 93 | 100, 259 |
| Diphenylene oxide | 2-Dibenzofuroyl | $CHCl_2:CHCl_2$ | 83 | 101 |
| | | + | | |
| Diphenylene oxide | 2-Dibenzofuroyl | $C_6H_5NO_2$ | 73, 90 † | 36 |
| Carbazole | Carbazole-3,6-bis- γ -ketobutyric acid (3,6-bis-carbazoyl) | Benzene | 54 | 102 |
| Carbazole | Carbazole-3,6-bis- γ -ketobutyric acid (3,6-bis-carbazoyl) | $C_6H_5NO_2$ | 91-94 | 103 |
| N-Methylcarbazole | N-Methylcarbazole-3,6-bis- γ -keto- butyric acid | $C_6H_5NO_2$ | — | 102 |
| 1-Nitro-3-phenylpropane | 4(?) ω -Nitropropylbenzoyl | CS_2 | 26.5 | 20 |
| Ethyl hydrocinnamate | 4(?) ω -Carbethoxyethylbenzoyl | CS_2 | 29 | 20 |
| 1-Cyano-2-phenylethane | 4 ω -Cyanoethylbenzoyl | CS_2 | 7.4 | 20 |
| Benzyl cyanide | No reaction | CS_2 | | 20 |
| Phenothiazine | N-Phenothiazoyl | CS_2 | 50 | 104 |
| N-Acetylphenothiazine | 2-Phenothiazoyl ‡ | CS_2 | 9 | 104 |
| <i>o</i> -Phenylenedurea | 3,4-Ureylenebenzoyl | $CHCl_2:CHCl_2$ | 9 | 233 |
| Acetanilide | 4-Acetylaminobenzoyl | CS_2 | 50-60 | 19 |
| <i>o</i> -Nitroanisole | 4-Methoxy-3-nitrobenzoyl | $C_6H_5NO_2$ | Low | 19 |
| 1-Acetyl-amino-7-methoxy-naphthalene | 1-Acetyl-amino-7-methoxy-3-naphthoyl | $C_6H_5NO_2$ | 84 | 259 |

* References 217-296 are on pp. 268-289.

† The 90% yield was obtained after refluxing for two hours.

‡ The primary product was probably the N-acetyl compound which was hydrolyzed during the isolation. The same compound was obtained in 58% yield with the ester acid chloride of succinic acid instead of the anhydride.

TABLE X
REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Reference * |
|--|--|----------------|--------------|-------------|
| <i>A. Methylsuccinic Anhydride</i> | | | | |
| Benzene | α -Methyl- β -benzoyl | Benzene | 39 | 120 |
| Benzene | α -Methyl- β -benzoyl | Benzene | 60 | 121 |
| Benzene | α -Methyl- β -benzoyl | Benzene | 49.5 | 7 |
| Benzene | α -Methyl- β -benzoyl | Benzene | — | 270 |
| Benzene | α -Methyl- β -benzoyl | Benzene | 75 | 122 |
| | β -methyl- β -benzoyl | Benzene | 12 | |
| Toluene | α -Methyl- β -p-tolyl | Toluene | 40.1 | 123 |
| | β -methyl- β -p-tolyl | | 37 | |
| Toluene | α -Methyl- β -p-tolyl | $C_6H_5NO_2$ | 85 | 254 |
| p-Cymene | α -Methyl- β -(2-methyl-5-isopropyl)benzoyl | $C_6H_5NO_2$ | 60 | 265 |
| Naphthalene | α -Methyl- β -1-naphthoyl and α -methyl- β -2-naphthoyl | $C_6H_5NO_2$ | 28 | 6 |
| | | | 27 | |
| 1-Methylnaphthalene | α -Methyl- β -(4-methyl-1-naphthoyl) | $C_6H_5NO_2$ | 75 | 124 |
| 2-Methylnaphthalene | α -Methyl- β -(6-methyl-2-naphthoyl) | $C_6H_5NO_2$ | 60 | 115 |
| 2-Isopropylnaphthalene | α -Methyl- β -(6-isopropyl-2-naphthoyl) | $C_6H_5NO_2$ | 21.5 | 276 |
| Phenanthrene | α -Methyl- β -3-phenanthroyl | $C_6H_5NO_2$ | 30 | |
| | α -methyl- β -2-phenanthroyl | | 3.3 | 123, 206 |
| Pyrene | α -Methyl- β -1-pyrenoyl | $C_6H_5NO_2$ | 90 | 47, 125 |
| Anisole | α -Methyl- β -p-anisoyl | $C_6H_5NO_2$ | 77 | 126 |
| Anisole | α -Methyl- β -p-anisoyl | $C_6H_5NO_2$ | 50 | 130 |
| o-Cresyl methyl ether | α -Methyl- β -(4-methoxy-3-tolyl) | $C_6H_5NO_2$ † | 40 | 127 |
| m-Cresyl methyl ether | α -Methyl- β -(4-methoxy-3-tolyl) | $C_6H_5NO_2$ ‡ | 20 | 127 |
| p-Cresyl methyl ether | α -Methyl- β -(2-methoxy-5-tolyl) | $C_6H_5NO_2$ ‡ | 33 | 127 |
| Veratrole | Mixture of α - and β -methyl- β -3,4-dimethoxybenzoyl | $C_6H_5NO_2$ | Quantitative | 129 |
| Veratrole | β -Methyl- β -3,4-dimethoxybenzoyl | $C_6H_5NO_2$ | 23.5 † | 128 |
| Resorcinol dimethyl ether | Mixture of α - and β -methyl- β -2,4-dimethoxybenzoyl | $C_6H_5NO_2$ | 50 | 126 |
| | α -Methyl- β -(2-hydroxy-3,4-dimethoxybenzoyl) and | | 10.2 ‡ | |
| Pyrogallol trimethyl ether | β -methyl- β -(3-hydroxy-3,4-dimethoxybenzoyl) | $C_6H_5NO_2$ | 3.4 | 126 |
| Phenol | α -Methyl- β -2-hydroxybenzoyl | $CHCl_3CHCl_3$ | 33 | 128 |
| Thiophene | α -Methyl- β -3-thienoyl | $C_6H_5NO_2$ | 6.6 | 290 |
| <i>B. sym-Dimethylsuccinic Anhydride</i> | | | | |
| Benzene | α,β -Dimethyl- β -benzoyl | Benzene | 85 | 15 |
| Veratrole | α,β -Dimethyl- β -3,4-dimethoxybenzoyl | $C_6H_5NO_2$ | 39 | 145 |
| Naphthalene | α,β -Dimethyl- β -(1-naphthoyl) | $C_6H_5NO_2$ | 17 † | 159 |

* References 217-296 are on pp. 288-289.

† The total yield of acids was 77%.

‡ In carbon disulfide or tetrachloroethane the yields were much lower.

§ The reaction furnished a mixture of the α -methyl and β -methyl acids from which only the latter was isolated.

|| The yield of the mixture before separation was 54%.

¶ The yield refers to a mixture of isomers.

TABLE IX

REACTIONS OF SUCCINIC ANHYDRIDE WITH HETEROCYCLES AND MISCELLANEOUS COMPOUNDS

| Starting Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|------------------------------------|--|-----------------|------------|------------------|
| Thiophene | 2-Thienoyl | $C_6H_5NO_2$ | 54; 58.5 | 94; 164 |
| Thiophene | 2-Thienoyl | CS_2 | 21 | 94 |
| 2,5-Dimethylthiophene | 2,5-Dimethyl-3-thienoyl | $C_6H_5NO_2$ | — | 95 |
| Benzothiophene (thionaphthene) | 3-Thionaphthoyl | $C_6H_5NO_2$ | 43 | 95 |
| Thiochromane | 6-Thiochromanoyl | $C_6H_5NO_2$ | 90 | 98 |
| Dibenzothiophene | 2-Dibenzothienoyl | $CHCl_3:CHCl_2$ | 66 | 97 |
| | | + | | |
| | | $C_6H_5NO_2$ | | |
| Dibenzothiophene | 2-Dibenzothienoyl | $C_6H_5NO_2$ | 61.5 | 95 |
| Diphenylene oxide | 2-Dibenzofuroyl | ? | — | 99 |
| Diphenylene oxide | 2-Dibenzofuroyl | $C_6H_5NO_2$ | 93 | 100, 259 |
| Diphenylene oxide | 2-Dibenzofuroyl | $CHCl_3:CHCl_2$ | 83 | 101 |
| | | + | | |
| | | $C_6H_5NO_2$ | | |
| Diphenylene oxide | 2-Dibenzofuroyl | Benzene | 73, 90 † | 25 |
| Carbazole | Carbazole-3,6-bis- γ -ketobutyric acid (3,6-bis-carbazoyl) | $C_6H_5NO_2$ | 54 | 102 |
| Carbazole | Carbazole-3,6-bis- γ -ketobutyric acid (3,6-bis-carbazoyl) | $C_6H_5NO_2$ | 91-94 | 103 |
| N-Methylcarbazole | N-Methylcarbazole-3,6-bis- γ -keto- butyric acid | $C_6H_5NO_2$ | — | 102 |
| 1-Nitro-3-phenylpropane | 4(7)- α -Nitropropylbenzoyl | CS_2 | 25.5 | 20 |
| Ethyl hydroxamate | 4(7)- α -Carbethoxyethylbenzoyl | CS_2 | 29 | 20 |
| 1-Cyano-2-phenylethane | 4- α -Cyanoethylbenzoyl | CS_2 | 7.4 | 20 |
| Benzyl cyanide | No reaction | CS_2 | | 20 |
| Phenothiazine | N-Phenothiazoyl | CS_2 | 50 | 104 |
| N-Acetylphenothiazine | 2-Phenothiazoyl ‡ | CS_2 | 9 | 104 |
| o-Phenylenediamine | 3,4-Terephenbenzoyl | $CHCl_3:CHCl_2$ | 9 | 223 |
| Acetanilide | 4-Acetylaminobenzoyl | CS_2 | 50-60 | 19 |
| o-Nitroaniline | 4-Methoxy-3-nitrobenzoyl | $C_6H_5NO_2$ | Low | 19 |
| 1-Acetylamine-7-methoxy-3-naphthol | 1-Acetylamine-7-methoxy-3-naphthoyl | $C_6H_5NO_2$ | 84 | 259 |

* References 217-256 are on pp. 255-259.

† The 90% yield was obtained after refluxing for two hours.

‡ The primary product was probably the N-acetyl compound which was hydrolyzed during the isolation. The same compound was obtained in 55% yield with the ester acid chloride of succinic acid instead of the anhydride.

TABLE X
REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Product β -Aroylpropionic Acid | Solvent | Yield % | Refer- ence * |
|------------------------------------|---|-----------------|--------------|------------------|
| <i>A. Methylsuccinic Anhydride</i> | | | | |
| benzene | α -Methyl- β -benzoyl | Benzene | 39 | 120 |
| benzene | α -Methyl- β -benzoyl | Benzene | 60 | 121 |
| benzene | α -Methyl- β -benzoyl | Benzene | 49.8 | 7 |
| benzene | α -Methyl- β -benzoyl | Benzene | — | 270 |
| benzene | α -Methyl- β -benzoyl | Benzene | 75 | 122 |
| benzene | β -methyl- β -benzoyl | Benzene | 13 | |
| toluene | α -Methyl- β -p-tolyl | Toluene | 40 † | 123 |
| toluene | β -methyl- β -p-tolyl | | 37 | |
| toluene | α -Methyl- β -p-tolyl | $C_6H_5NO_2$ | 86 | 254 |
| toluene | α -Methyl- β -(2-methyl-5-isopropylbenzoyl) | $C_6H_5NO_2$ | 60 | 253 |
| naphthalene | α -Methyl- β -1-naphthyl and α -methyl- β -2-naphthyl | $C_6H_5NO_2$ | 28 | 6 |
| | | | 27 | |
| 1-methylnaphthalene | α -Methyl- β -(4-methyl-1-naphthyl) | $C_6H_5NO_2$ | 75 | 124 |
| 1-methylnaphthalene | α -Methyl- β -(6-methyl-2-naphthyl) | $C_6H_5NO_2$ | 60 | 115 |
| 1-isopropylnaphthalene | α -Methyl- β -(4-isopropyl-2-naphthyl) | $C_6H_5NO_2$ | 21.8 | 273 |
| phenanthrene | α -Methyl- β -3-phenanthryl | $C_6H_5NO_2$ | 30 | 125, 208 |
| | α -methyl- β -3-phenanthryl | | 9.8 | |
| pyrene | α -Methyl- β -1-pyrenyl | $C_6H_5NO_2$ | 90 | 47, 126 |
| quinoline | α -Methyl- β -quinolyl | $C_6H_5NO_2$ | 77 | 126 |
| quinoline | α -Methyl- β -quinolyl | $C_6H_5NO_2$ | 30 | 130 |
| 2-methyl-3-phenyl ether | α -Methyl- β -(4-methoxy-3-tolyl) | $C_6H_5NO_2$ ‡ | 40 | 127 |
| 2-methyl-3-phenyl ether | α -Methyl- β -(4-methoxy-3-tolyl) | $C_6H_5NO_2$ ‡ | 20 | 127 |
| 2-methyl-3-phenyl ether | α -Methyl- β -(2-methoxy-6-tolyl) | $C_6H_5NO_2$ ‡ | 33 | 127 |
| 2-methyl-3-phenyl ether | Mixture of α - and β -methyl- β -3,4-dimethoxy- benzoyl | $C_6H_5NO_2$ | Quantitative | 129 |
| 2-methyl-3-phenyl ether | β -Methyl- β -3,4-dimethoxybenzoyl | $C_6H_5NO_2$ | 23.4 † | 128 |
| 2-methyl-3-phenyl ether | Mixture of α - and β -methyl- β -3,4-dimethoxy- benzoyl | $C_6H_5NO_2$ | 80 | 128 |
| 2-methyl-3-phenyl ether | α -Methyl- β -(2-hydroxy-3,4-dimethoxyben- zoyl) and β -methyl- β -(2-hydroxy-3,4-dimethoxyben- zoyl) | $C_6H_5NO_2$ | 10.2 ‡ | 129 |
| 2-methyl-3-phenyl ether | α -Methyl- β -(2-hydroxybenzoyl) | $CHCl_3/CHCl_3$ | 23 | 175 |
| 2-methyl-3-phenyl ether | α -Methyl- β -3-thienyl | $C_6H_5NO_2$ | 6.6 | 200 |

B. sym-Dimethylsuccinic Anhydride

| | | | | |
|---------------|--|--------------|------|-----|
| benzene | α, β -Dimethyl- β -benzoyl | Benzene | 85 | 18 |
| benzene | α, β -Dimethyl- β -3,4-dimethoxybenzoyl | $C_6H_5NO_2$ | 39 | 245 |
| 1-naphthalene | α, β -Dimethyl- β -(1-naphthyl) | $C_6H_5NO_2$ | 17.5 | 199 |

* References 217-256 are on pp. 258-283.

† The total yield of acids was 77%.

‡ In carbon disulfide or tetrachloroethane the yields were much lower.

§ The reaction furnished a mixture of the α -methyl and β -methyl acids from which only the latter was isolated.

|| The yield of the mixture before separation was 54%.

¶ The yield refers to a mixture of isomers.

TABLE X—Continued

REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Product <i>β</i> -Arylsuccinic Acid | Solvent | Yield % | Reference* |
|-------------------|--|---------|------------|------------|
|-------------------|--|---------|------------|------------|

C. *αα*-Dimethylsuccinic Anhydride

| | | | | |
|--------------------------------|--|---|------|-----|
| Benzene | <i>αα</i> -Dimethyl- <i>β</i> -benzoyl | Benzene | — | 137 |
| Benzene | <i>αα</i> -Dimethyl- <i>β</i> -benzoyl | Benzene | 53 | 15 |
| Benzene | <i>αα</i> -Dimethyl- <i>β</i> -benzoyl | Benzene | 62 | 138 |
| Benzene | <i>αα</i> -Dimethyl- <i>β</i> -benzoyl | Benzene | 50 | 15 |
| Benzene | <i>αα</i> -Dimethyl- <i>β</i> -benzoyl | C ₆ H ₅ NO ₂ | 50 | 14 |
| Toluene | <i>αα</i> -Dimethyl- <i>β</i> -tolyl | Toluene | 77.5 | 133 |
| Hydrotolene | <i>αα</i> -Dimethyl- <i>β</i> -hydrotolyl | C ₆ H ₅ NO ₂ | 21 | 55 |
| Naphthalene | (<i>αα</i> -Dimethyl- <i>β</i> -1-naphthyl, <i>αα</i> -dimethyl- <i>β</i> -2-naphthyl) | C ₆ H ₅ NO ₂ | 25† | 139 |
| 1-Methyl- <i>n</i> -aphthalene | <i>αα</i> -Dimethyl- <i>β</i> -(1-methyl-4-naphthyl) | C ₆ H ₅ NO ₂ | 72 | 139 |

D. Triethylsuccinic Anhydride

| | | | | |
|---------|---|---------|--------|----|
| Benzene | <i>ααβ</i> -Triethyl- <i>β</i> -benzoyl | Benzene | 53, 53 | 15 |
|---------|---|---------|--------|----|

E. *αα*-Methylsuccinic Anhydride

| | | | | |
|-------------|---|---|----|-----|
| Benzene | <i>α</i> -Methyl- <i>α</i> -ethyl- <i>β</i> -benzoyl | Benzene | — | 137 |
| Naphthalene | <i>α</i> -Methyl- <i>α</i> -ethyl- <i>β</i> -(1-naphthyl) | C ₆ H ₅ NO ₂ | 41 | 140 |

F. *ααα*-Diethylsuccinic Anhydride

| | | | | |
|---------|--|---------|----|-----|
| Acetone | <i>ααβ</i> -Diethyl- <i>β</i> -benzoyl | Benzene | 57 | 144 |
|---------|--|---------|----|-----|

G. *ααα*-Diethylsuccinic Anhydride

| | | | | |
|---------|--|---------|------|-----|
| Benzene | <i>ααα</i> -Diethyl- <i>β</i> -benzoyl | Benzene | 62.3 | 138 |
|---------|--|---------|------|-----|

H. Tetraethylsuccinic Anhydride

| | | | | |
|---------|---|---------|----|----|
| Benzene | <i>αααβ</i> -Tetraethyl- <i>β</i> -benzoylpropionate and 17 | Benzene | 77 | 16 |
| Toluene | <i>αααβ</i> -Tetraethyl- <i>β</i> -benzoylpropionate and 17 | Toluene | — | 19 |

* References 137-140 are on pp. 246-267.

† The yield of the mixture was 100%.

TABLE X—Continued
REACTIONS OF SUBSTITUTED SUCCHINIC ANHYDRIDES

| Aromatic Compound | Substituent in Anhydride | Product β -Arylpropionic Acid | Solvent | Yield % | Reference * |
|---|--------------------------|--|--------------|---------|-------------|
| <i>I. Mono-α-alkylsuccinic Anhydrides</i> | | | | | |
| Anisole | Ethyl | α -Ethyl- β -anisoyl | $C_6H_5NO_2$ | 79 | 130 |
| Anisole | Propyl | α -Propyl- β -anisoyl | $C_6H_5NO_2$ | 62 | 130 |
| Anisole | Amyl | α -Amyl- β -anisoyl | $C_6H_5NO_2$ | 30 | 130 |
| Anisole | Hexyl | α -Hexyl- β -anisoyl | $C_6H_5NO_2$ | 45 | 130 |
| Anisole | Tetradecyl | α -Tetradecyl- β -anisoyl | $C_6H_5NO_2$ | 60 | 130 |
| Anisole | Hexadecyl | α -Hexadecyl- β -anisoyl | $C_6H_5NO_2$ | 50 | 130 |
| α -Cresyl methyl ether | Ethyl | α -Ethyl- β -(4-methoxy-3-methylbenzoyl) | $C_6H_5NO_2$ | 40 | 277 |
| α -Cresyl methyl ether | Propyl | α -Propyl- β -(4-methoxy-3-methylbenzoyl) | $C_6H_5NO_2$ | 45 | 277 |
| α -Cresyl methyl ether | Amyl | α -Amyl- β -(4-methoxy-3-methylbenzoyl) | $C_6H_5NO_2$ | 30 | 277 |

J. Aromatically Substituted Succinic Anhydrides

| | | | | | |
|---------|-------------------------|---|--------------|---------------------|-----|
| Benzene | Phenyl | β -Phenyl- β -benzoyl | Benzene | — | 131 |
| Benzene | Phenyl | Equal mixture of α - and β -phenyl- β -benzoyl | Benzene | — | 15 |
| Benzene | Phenyl | Mixture of α - and β -phenyl- β -benzoyl | Benzene | 65 | 14 |
| Benzene | Phenyl | α -Phenyl- β -benzoyl | Benzene | 43 | 17 |
| | | β -phenyl- β -benzoyl | | 52 | |
| Benzene | Phenyl | α -Phenyl- β -benzoyl | $C_6H_5NO_2$ | 80 | 17 |
| | | β -phenyl- β -benzoyl | | 11 | |
| Benzene | <i>p</i> -Nitrophenyl | α - <i>p</i> -Nitrophenyl- β -benzoyl | Benzene | 45 | 17 |
| | | β - <i>p</i> -nitrophenyl- β -benzoyl | | 55 | |
| Benzene | <i>p</i> -Nitrophenyl | α - <i>p</i> -Nitrophenyl- β -benzoyl | $C_6H_5NO_2$ | 5 | 17 |
| | | β - <i>p</i> -nitrophenyl- β -benzoyl | | 95 | |
| Benzene | <i>p</i> -Methoxyphenyl | α - <i>p</i> -Methoxyphenyl- β -benzoyl | Benzene | Nearly quantitative | 17 |
| | | | | quantitative | |
| Benzene | <i>p</i> -Methoxyphenyl | α - <i>p</i> -Methoxyphenyl- β -benzoyl | $C_6H_5NO_2$ | Nearly quantitative | 17 |
| | | | | quantitative | |
| Benzene | <i>p</i> -Chlorophenyl | α - <i>p</i> -Chlorophenyl- β -benzoyl | Benzene | 46 | 17 |
| | | β - <i>p</i> -chlorophenyl- β -benzoyl | | 54 | |
| Benzene | <i>p</i> -Chlorophenyl | α - <i>p</i> -Chlorophenyl- β -benzoyl | $C_6H_5NO_2$ | Quant. | 17 |
| | | | | 20† | |
| Toluene | Phenyl | α -Phenyl- β - <i>p</i> -tolyl | Toluene | 33 | 16 |
| | | β -phenyl- β - <i>p</i> -tolyl | | 23 | |
| Toluene | Phenyl | α -Phenyl- β - <i>p</i> -tolyl | Toluene | 77 | 17 |
| | | β -phenyl- β - <i>p</i> -tolyl | | 45‡ | |
| Toluene | Phenyl | α -Phenyl- β - <i>p</i> -tolyl | $C_6H_5NO_2$ | 7.0 | 16 |

* References 217-276 are on pp. 253-289.

† The yield of the mixture was 69%. ‡ The yield of the mixture was 71%.

TABLE X—Continued
REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Substituent in Anhydride | Product β -Arylpropionic Acid | Solvent | Yield % | Refer- ence * |
|-----------------------|--------------------------|--|-----------------------------------|------------------------|------------------|
| Toluene (Continued) | Phenyl | α -Phenyl- β -p-toluyyl, β -phenyl- β -p-toluyyl | $C_6H_5NO_2$ | 83 17 | 17 |
| Toluene | p-Nitrophenyl | α -p-Nitrophenyl- β -p-toluyyl, β -p-nitrophenyl- β -p-toluyyl | Toluene | 20 80 | 17 |
| Toluene | p-Nitrophenyl | α -p-Nitrophenyl- β -p-toluyyl, β -p-nitrophenyl- β -p-toluyyl | $C_6H_5NO_2$ | 33 67 | 17 |
| Toluene | p-Methoxyphenyl | α -p-Methoxyphenyl- β -p-toluyyl, β -p-methoxyphenyl- β -p-toluyyl | Toluene | 82 18 | 17 |
| Toluene | p-Methoxyphenyl | α -p-Methoxyphenyl- β -p-toluyyl | $C_6H_5NO_2$ | Pre- pond- erant | 17 |
| Biphenyl | Phenyl | β -Phenyl- β -p-phenylbenzoyl | CS_2 | — | 136 |
| Anisole | o-Methoxyphenyl | α -o-Methoxyphenyl- β -p-anisoyl | $CHCl_2CHCl_2$ or $C_6H_5NO_2$ | — | 261 |
| Anisole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -p-anisoyl | CS_2 | 35 | 133 |
| Anisole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -p-anisoyl | $CHCl_2CHCl_2$ | 95 † | 133 |
| Anisole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -p-anisoyl | $C_6H_5NO_2$ | 77 | 133 |
| o-Cresyl methyl ether | o-Methoxyphenyl | α -o-Methoxyphenyl- β -(4- methoxy-3-methylbenzoyl), β -o-methoxyphenyl- β -(4- methoxy-3-methylbenzoyl) | $C_6H_5NO_2$ | 44 49 | 132 |
| o-Cresyl methyl ether | o-Methoxyphenyl | α -o-Methoxyphenyl- β -(4- methoxy-3-methylbenzoyl), β -o-methoxyphenyl- β -(4- methoxy-3-methylbenzoyl) | $CHCl_2CHCl_2$ | 54 42 | 132 |
| o-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-3-methylbenzoyl) | CS_2 | 65 | 133 |
| o-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-3-methylbenzoyl) | $CHCl_2CHCl_2$ | 95 | 133 |
| o-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-3-methylbenzoyl) | $C_6H_5NO_2$ | 92 | 133 |
| m-Cresyl methyl ether | o-Methoxyphenyl | α -o-Methoxyphenyl- β -(4- methoxy-2-methylbenzoyl), β -o-methoxyphenyl- β -(4- methoxy-2-methylbenzoyl) | $C_6H_5NO_2$ | 60 20 | 132 |
| m-Cresyl methyl ether | o-Methoxyphenyl | α -o-Methoxyphenyl- β -(4- methoxy-2-methylbenzoyl), β -o-methoxyphenyl- β -(4- methoxy-2-methylbenzoyl) | $CHCl_2CHCl_2$ | 59 27 | 132 |
| m-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-2-methylbenzoyl) | CS_2 | 15 | 133 |
| m-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-2-methylbenzoyl) | $CHCl_2CHCl_2$ | 90 | 133 |
| m-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(4- methoxy-2-methylbenzoyl) | $C_6H_5NO_2$ | 75 | 133 |
| p-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3- methoxy-5-methylbenzoyl) | CS_2 | 10 | 133 |

* References 217–296 are on pp. 283–289.

† Another isomer was formed in small amount.

TABLE X—Continued
 REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Substituent in Anhydride | Product β -Arylsuccinic Acid | Solvent | Yield % | Reference * |
|--------------------------------------|--------------------------|---|--|---------|-------------|
| p-Cresyl methyl ether (Continued) | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3-methoxy-5-methylbenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ | 90 | 133 |
| p-Cresyl methyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3-methoxy-5-methylbenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ † | 45 | 133 |
| Veratrole | Phenyl | α -Phenyl- β -(3,4-dimethoxybenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 84 | 133 |
| Veratrole | α -Methoxyphenyl | α - α -Methoxyphenyl- β -(3,4-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ or $\text{C}_6\text{H}_5\text{NO}_2$ | — | 261 |
| Veratrole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3,4-dimethoxybenzoyl) | CS_2 | — | 134 |
| Veratrole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3,4-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ | 85 | 134 |
| Veratrole | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3,4-dimethoxybenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 64 | 134 |
| Guaiaol | p-Methoxyphenyl | No reaction | CS_2 $\text{CHCl}_3\text{CHCl}_3$ $\text{C}_6\text{H}_5\text{NO}_2$ | — | 134 |
| Resorcinol dimethyl ether | α -Methoxyphenyl | α - α -Methoxyphenyl- β -(2,4-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ or $\text{C}_6\text{H}_5\text{NO}_2$ | — | 261 |
| Resorcinol dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,4-dimethoxybenzoyl) | CS_2 | 85 | 134 |
| Resorcinol dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,4-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ | 65 | 134 |
| Resorcinol dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,4-dimethoxybenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 64 | 134 |
| Resorcinol dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,4-dimethoxybenzoyl) | CS_2 | 80 ‡ | 132 |
| Resorcinol dimethyl ether | 2,4-Dimethoxyphenyl | α -2,4-Dimethoxyphenyl- β -(2,4-dimethoxybenzoyl) | CS_2 | 40 | 134 |
| Resorcinol monomethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3-hydroxy-4-methoxybenzoyl) | CS_2 | 71 | 134 |
| Resorcinol monomethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3-hydroxy-4-methoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ | 73 | 134 |
| Resorcinol monomethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(3-hydroxy-4-methoxybenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 89 | 134 |
| Hydroquinone dimethyl ether | α -Methoxyphenyl | α - α -Methoxyphenyl- β -(2,5-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ or $\text{C}_6\text{H}_5\text{NO}_2$ | — | 261 |
| Hydroquinone dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,5-dimethoxybenzoyl) | CS_2 | — | 134 |
| Hydroquinone dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,5-dimethoxybenzoyl) | $\text{CHCl}_3\text{CHCl}_3$ | 14 | 134 |
| Hydroquinone dimethyl ether | p-Methoxyphenyl | α -p-Methoxyphenyl- β -(2,5-dimethoxybenzoyl) | $\text{C}_6\text{H}_5\text{NO}_2$ | 29 | 134 |
| Hydroquinone monomethyl ether | p-Methoxyphenyl | No reaction | CS_2 $\text{CHCl}_3\text{CHCl}_3$ $\text{C}_6\text{H}_5\text{NO}_2$ | — | 134 |

* References 217-266 are on pp. 268-269.

† In nitrobenzene 45% of an isomer was formed.

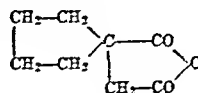
‡ The total yield of pure mixed product was 63%.

TABLE X—Continued

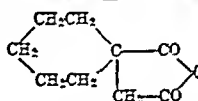
REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Product β -Arylpropionic Acid | Solvent | Yield % | Reference * |
|-------------------|--|---------|---------|-------------|
|-------------------|--|---------|---------|-------------|

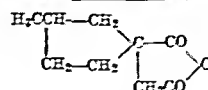
K. Miscellaneous Substituted Succinic Anhydrides

Cyclopentane-1-carboxy-1-acetic Acid Anhydride
(1,1-Spirocyclopentane Succinic Anhydride)

| | | | | |
|----------------------|--|---|-----|-----|
| Benzene | $\alpha\alpha$ -Spirocyclopentane- β -benzoyl † | Benzene | 60 | 252 |
| Benzene | $\alpha\alpha$ -Spirocyclopentane- β -benzoyl | Benzene | — | 14 |
| Toluene | $\alpha\alpha$ -Spirocyclopentane- β -p-tolyl | Toluene | 77 | 141 |
| Ethylbenzene | $\alpha\alpha$ -Spirocyclopentane- β -p-ethylbenzoyl | CS ₂ | 74 | 141 |
| Hydrotene | $\alpha\alpha$ -Spirocyclopentane- β -5-hydroxyethyl | C ₆ H ₅ NO ₂ | — | 143 |
| Naphthalene | $\alpha\alpha$ -Spirocyclopentane- β -1-naphthyl and $\alpha\alpha$ -Spirocyclopentane- β -2-naphthyl | C ₆ H ₅ NO ₂ | 9.7 | 142 |
| 1-Methyl-naphthalene | $\alpha\alpha$ -Spirocyclopentane- β -(4-methyl-1-naphthyl) | C ₆ H ₅ NO ₂ | 3.7 | 142 |
| | | | 39 | 142 |

Cyclohexane-1-carboxy-1-acetic Acid Anhydride
(1,1-Spirocyclohexane Succinic Anhydride)

| | | | | |
|--------------|---|---|------|-----|
| Benzene | $\alpha\alpha$ -Spirocyclohexane- β -benzoyl | Benzene | 55 | 15 |
| Benzene | $\alpha\alpha$ -Spirocyclohexane- β -benzoyl | Benzene | — | 252 |
| Benzene | $\alpha\alpha$ -Spirocyclohexane- β -benzoyl | C ₆ H ₅ NO ₂ | Poor | 15 |
| Toluene | $\alpha\alpha$ -Spirocyclohexane- β -p-tolyl | Toluene | 55 | 15 |
| Toluene | $\alpha\alpha$ -Spirocyclohexane- β -p-tolyl | Toluene(?) | — | 252 |
| Toluene | $\alpha\alpha$ -Spirocyclohexane- β -p-tolyl and 1,1-spirocyclohexane-1,2-di-p-tolylolethane | C ₆ H ₅ NO ₂ | — | 15 |
| Ethylbenzene | $\alpha\alpha$ -Spirocyclohexane- β -p-ethylbenzoyl | Ethylbenzene(?) | 29 | 252 |

2-Methylcyclopentane-1-carboxy-1-acetic Acid Anhydride
(1,1-Cypro-3-methylcyclopentane)succinic Anhydride)

| | | | | |
|---------|--|---|------|----|
| Benzene | $\alpha\alpha$ -Spiro-(3-methylcyclopentane)- β -benzoyl | Benzene | 53 | 15 |
| Benzene | $\alpha\alpha$ -Spiro-(3-methylcyclopentane)- β -benzoyl | C ₆ H ₅ NO ₂ | Poor | 15 |
| Toluene | $\alpha\alpha$ -Spiro-(3-methylcyclopentane)- β -p-tolyl | Toluene | 73 | 15 |

 $\Delta^1,2$ -Cyclopentane-1,2-dicarboxylic Acid Anhydride

| | | | | |
|-------------|--|---|---|-----|
| Naphthalene | $\Delta^1,2$ -Cyclopentane-1-(1- and 2-naphthyl)-2-carboxylic acid | C ₆ H ₅ NO ₂ | — | 142 |
|-------------|--|---|---|-----|

* References 217-225 are on pp. 253-259.

† This compound was first considered to be the $\beta\beta$ -isomer. See ref. 14.

TABLE X—Continued
REACTIONS OF SUBSTITUTED SUCCINIC ANHYDRIDES

| Aromatic Compound | Product | Solvent | Yield % | Reference * |
|--|---|---------|---------|-------------|
| <i>cis</i> -Hexahydrophthalic Anhydride | | | | |
| Benzene | 3-Benzoylcyclohexane-1-carboxylic acid | Benzene | 90 | 263 |
| <i>cis</i> -3,6-Endomethylenecyclohexanedicarboxylic Anhydride | | | | |
| Benzene | 3-Benzoylacromaphane-3-carboxylic acid | Benzene | 87 | 264 |
| Bromosuccinic Anhydride | | | | |
| Benzene | α -Bromo- β -benzoylpropionic acid | Benzene | 80 | 135 |
| Isobromosuccinic Anhydride | | | | |
| Benzene | Isobromo- β -benzoylpropionic acid | Benzene | 80-85 | 177 |
| Benzene | Isobromo- β -benzoylpropionic acid | Benzene | — | 263 |

* References 217-206 are on pp. 233-239.

TABLE XI
REACTIONS OF GLUTARIC ANHYDRIDE

| Aromatic Compound | Product γ -Aroylbutyric Acid | Solvent | Yield % | Reference * |
|----------------------------|---|--|------------|-------------|
| Benzene | Benzoyl | Benzene | 72 | 15 |
| Benzene | Benzoyl | Benzene | 80-85 | 204 |
| Benzene | Benzoyl | Benzene | 24 | 148 |
| | 1,2-dibenzoylpropane | | 18.5 | |
| Toluene | p-Toloyl | | 63 | |
| | 1,3-di-p-toloylpropane | $\text{CHCl}_3\text{CHCl}_2$ | 15.2 | 149 |
| Tetrahn | 2-Tetroyl | Benzene | 43 | 28 |
| Acenaphthene | 2-Acenaphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | Poor | 29 |
| Anisole | 4-Anisoyl | CS_2 | — | 150 |
| Anisole | 4-Anisoyl | Anisole | 75 | 151 |
| Anisole | 4-Anisoyl | $\text{CHCl}_3\text{CHCl}_2 + \text{C}_6\text{H}_5\text{NO}_2$ | 85 | 26 |
| Anisole | 4-Anisoyl | $\text{CHCl}_3\text{CHCl}_2 + \text{C}_6\text{H}_5\text{NO}_2$ | 82 | 294 |
| Phenetole | 4-Ethoxybenzoyl | CS_2 | — | 150 |
| Phenetole | 4-Ethoxybenzoyl | Phenetole | 64 | 152 |
| Diphenyl ether | 4-Phenoxybenzoyl | Benzene | 84.5 | 93 |
| Diphenyl ether | 4-Phenoxybenzoyl | CS_2 | Poor | 93 |
| Veratrole | 3,4-Dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 45 | 153 |
| Pyrogallol trimethyl ether | 2,3,4-Trimethoxybenzoyl and a small amount of a γ -(hydroxydimethoxybenzoyl)butyric acid | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 155 |
| Chlorobenzene | p-Chlorobenzoyl | CS_2 | Low | 20 |
| Thiophene | 2-Thiroyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 39.4 | 154 |
| o-Phenylenesulfone | 3,4-Treylenebenzoyl | $\text{CHCl}_3\text{CHCl}_2$ | 5 | 253 |

* References 217-226 are on pp. 282-289.

TABLE XII
REACTIONS OF SUBSTITUTED GLUTARIC ANHYDRIDES

| Aromatic Compound | Substituent in Anhydride | Product γ -Arylbutyric Acid | Solvent | Yield % | Reference * |
|-------------------|--|--|---------|--------------|-------------|
| Benzene | β,β -Dimethyl | β,β -Dimethyl- γ -benzoyl | Benzene | Quantitative | 15 |
| Benzene | β -Methyl- β -ethyl | β -Methyl- β -ethyl- γ -benzoyl | Benzene | — | 15 |
| Benzene | β -Phenyl | Ketohydrondene-3-acetic acid † | Benzene | — | 15 |
| Benzene | β,β -Spirocyclopentyl ‡ | β,β -Spirocyclopentane- γ -benzoyl | Benzene | 61 | 15 |
| Benzene | β,β -Spirocyclohexyl § | β,β -Spirocyclohexane- γ -benzoyl | Benzene | — | 15 |
| Benzene | β,β -Spiro-(3-methylcyclopentyl) | β,β -Spiro-(3-methylcyclopentane)- γ -benzoyl | Benzene | — | 15 |

Camphoric Anhydride

| | | | | |
|---------|---|---------|---|-----|
| Benzene | 1,1,2-Trimethyl-2-phenylcyclopentane-5-carboxylic acid † | Benzene | — | 159 |
| Toluene | 1,1,2-Trimethyl-2(or 5)-toluylcyclopentane-5 (or 2)-carboxylic acid | Toluene | — | 160 |
| Anisole | 1,1,2-Trimethyl-2 (or 5)-anisoylcyclopentane-5 (or 2)-carboxylic acid | Anisole | — | 160 |

* References 217-226 are on pp. 233-239.

† This acid is formed by cyclization of the anhydride. See ref. 15c.

‡ Formula XIV on p. 243.

§ Formula XV on p. 243.

|| Phenylcamphoric acid. Carbon monoxide is lost in this reaction.

TABLE XIII
REACTIONS OF POLYMERIC ACID ANHYDRIDES *

| Aromatic Compound | Product | Solvent | Yield % | Reference † |
|--------------------------------------|--|---|--------------|-------------|
| <i>A. Polydicarboxylic Anhydride</i> | | | | |
| Benzene | ω -Benzoylvaleric acid, 1,4-dibenzoylbutane | Benzene | 75; 62 85 | 161, 36 |
| n-Butylbenzene | ω -n-Butylbenzoylvaleric acid | n-Butylbenzene | — | 272 |
| sec-Butyl-naphthalene | ω -sec-Butyl-naphthoylvaleric acid | sec-Butyl-naphthalene | — | 272 |
| Anisole | ω -p-Anisoylvaleric acid, 1,4-di-p-anisoylbutane | CS ₂ | 43 55 | 162 |
| Anisole | ω -p-Anisoylvaleric acid, 1,4-di-p-anisoylbutane | CHCl ₃ :CHCl ₂ + C ₆ H ₅ NO ₂ | 33 47 | 234 |
| Phenetole | ω -p-Ethoxybenzoylvaleric acid, 1,4-di-p-ethoxybenzoylbutane | CS ₂ | — | 162 |
| Thiophene ‡ | ω -2-Thienoylvaleric acid | Benzene | 3.6 | 164 |
| <i>B. Polycyclic Anhydride</i> | | | | |
| Thiophene ‡ | ω -2-Thienoylheptanoic acid, 1,6-di-2-thienoylhexane | Benzene | — 29.8 | 163, 164 |
| <i>C. Polydicarboxylic Anhydride</i> | | | | |
| Benzene | ω -Benzoyloctanoic acid | Benzene | 25 | 30 |
| Thiophene ‡ | ω -2-Thienoyloctanoic acid, 1,7-di-2-thienoylheptane | Benzene | 24.5 27 | 164 |
| <i>D. Polycyclic Anhydride</i> | | | | |
| Benzene | ω -Benzoylnonanoic acid, 1,8-dibenzoyloctane | Benzene | 78 86 | 161 |
| sec-Amylbenzene | ω -sec-Amylbenzoylnonanoic acid | sec-Amylbenzene | — | 272 |
| sec-Octyltoluene | ω -sec-Octyltoluylnonanoic acid | sec-Octyltoluene | — | 272 |
| Tetralin | ω -2-Tetroylnonanoic acid | C ₆ H ₅ NO ₂ | 40 ‡ | 36 |
| Thiophene ‡ | ω -2-Thienoylnonanoic acid, 1,8-di-2-thienoyloctane | Benzene | 8.2 21.2 | 164 |

* The yields are calculated on the basis of the equation on p. 248.

† References 217-256 are on pp. 283-289.

‡ Stannic chloride was used as the catalyst.

§ This yield refers to a crude product.

TABLE XIV
REACTIONS OF MALEIC ANHYDRIDE

| Aromatic Compound | Product β -Arylacrylic Acid | Solvent | Yield % | Reference * |
|--------------------------------|---|-----------------------------|------------|---------------------|
| Benzene | Benzoyl | Benzene | — | 2, 174, 177, 183 |
| Benzene | Benzoyl | Benzene | 67 † | 3 |
| Benzene | Benzoyl | Benzene | About 55 | 179 |
| Benzene | Benzoyl | Benzene | 85 | 178 |
| Benzene | Benzoyl | Benzene | 91 | 176a |
| Benzene | Benzoyl | Benzene | 15 | 183 |
| Benzene | <i>o</i> -Phenyl- β -benzoylpropionic acid ‡ | Benzene | 62 | 176a |
| Chlorobenzene | 4-Chlorobenzoyl | C_6H_5Cl | 90 | 176a |
| Bromobenzene | 4-Bromobenzoyl | C_6H_5Br | 72 | 290 |
| Bromobenzene | 4-Bromobenzoyl | $CHBr_3/CHCl_3$ | 74 | 291 |
| Bromobenzene | <i>trans</i> - β -(4-Bromobenzoyl) | $CHCl_3/CHCl_3$ | 10 | 176a |
| Iodobenzene | 4-Iodobenzoyl | $CHCl_3/CHCl_3$ | 55 | 176a |
| 1,3-Dichlorobenzene | 3,4-Dichlorobenzoyl | $C_6H_3Cl_2$ (1,2) | 17 | 176a |
| 1,3-Dichlorobenzene | 2,4-Dichlorobenzoyl | $CHCl_3/CHCl_3$ | — | 3 |
| Toluene | <i>p</i> -Tolyl | Toluene | <50 | 179 |
| Toluene | <i>p</i> -Tolyl | Toluene | 77 | 178 |
| Toluene | <i>p</i> -Tolyl | $CHCl_3/CHCl_3$ | 70-75 | 171 |
| Toluene | <i>p</i> -Tolyl | $CHCl_3/CHCl_3$ | 65 | 176a |
| Toluene | <i>p</i> -Tolyl | Toluene | 18 | 183 |
| Toluene | <i>o</i> - <i>p</i> -Tolyl- β -(<i>p</i> -tolyl)propionic acid ‡ | Toluene | 30 | 176a |
| <i>o</i> -Chlorotoluene | 3-Methyl-4-chlorobenzoyl | $CHCl_3/CHCl_3$ | 39 | 176a |
| <i>p</i> -Chlorotoluene | 3-Chloro-5-methylbenzoyl | $CHCl_3/CHCl_3$ | Approx. 25 | 179 |
| <i>m</i> -Xylene | 2,4-Dimethylbenzoyl | <i>m</i> -Xylene | 41 | 171 |
| <i>m</i> -Xylene | 2,4-Dimethylbenzoyl | $CHCl_3/CHCl_3$ | 91 | 176a |
| <i>m</i> -Xylene | 2,4-Dimethylbenzoyl | $CHCl_3/CHCl_3$ | 70-75 | 171 |
| <i>p</i> -Xylene | 2,5-Dimethylbenzoyl | $CHCl_3/CHCl_3$ | 90 | 176a |
| <i>p</i> -Xylene | 2,5-Dimethylbenzoyl | $CHCl_3/CHCl_3$ | 55 | 176a |
| Isopropylbenzene | 4-Isopropylbenzoyl | Monotoluene | — | 179 |
| Monotoluene | 2,4,6-Trimethylbenzoyl | $CHCl_3/CHCl_3$ | 62.5 | 292 |
| Monotoluene | <i>trans</i> - β -(2,4,6-Trimethylbenzoyl) | 1,3,4-Trimethylbenzene | — | 179 |
| 1,3,4-Trimethylbenzene | 2,4,5-Trimethylbenzoyl | <i>o</i> -tert-Butyltoluene | — | 180 |
| <i>o</i> -tert-Butyltoluene | 4-(or 5)Methyl-3-(or 4)-tert-butylbenzoyl | <i>p</i> -tert-Butyltoluene | — | 180 |
| <i>p</i> -tert-Butyltoluene | 2-Methyl-5-tert-butylbenzoyl and 3-methyl-5-tert-butylbenzoyl | <i>sec</i> -Amylbenzene | — | 272 |
| <i>sec</i> -Amylbenzene | <i>sec</i> -Amylbenzoyl | <i>sec</i> -Octylbenzene | — | 272 |
| <i>sec</i> -Octylbenzene | <i>sec</i> -Octylbenzoyl | CS_2 | — | 31 |
| <i>p</i> -Di-tert-butylbenzene | <i>p</i> -tert-Butylbenzoyl | $CHCl_3/CHCl_3$ | 45 ‡ | 176a |
| <i>p</i> -Di-tert-butylbenzene | 2,5-Di- <i>p</i> -tert-butylbenzoyl | $CHCl_3/CHCl_3$ | 63 | 176a |
| Phenylcyclohexane | 4-Cyclohexylbenzoyl | Benzene † | — | 178 |
| Naphthalene | A mixture containing mainly 2-naphthoyl | Benzene | 40 ‡ | 177 |
| Naphthalene | 1-Naphthoyl and 2-naphthoyl | Benzene | 60 | 176a |
| Tetralin | <i>p</i> -Tetrahydronaphthoyl | $CHCl_3/CHCl_3$ | 50 | 178 |
| Euphenyl | 4-Phenylbenzoyl | Benzene | 80 | 39 |
| Acenaphthene | 5-Acenaphthoyl | $C_6H_5NO_2$ | 32 | |

* References 217-206 are on pp. 288-289.

† The yield of pure acid was 50%.

‡ This acid was obtained only with an excess of aluminum chloride.

§ The product was isolated as the methyl ester.

|| In nitrobenzene no product could be isolated; see ref. 39.

¶ The total yield of the mixture was 70-80%.

TABLE XIV—Continued
 REACTIONS OF MALEIC ANHYDRIDE

| Aromatic Compound | Product <i>β</i> -Aroylacrylic Acid | Solvent | Yield % | Reference * |
|---------------------------------------|--|-----------------------------------|------------|-------------|
| Anthracene | 9-Anthroyl † | Benzene | 44 | 175 |
| Anisole | 4-Anisoyl | (?) | — | 175 |
| Anisole | 4-Anisoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 27 | 171 |
| Anisole | 4-Anisoyl | CS_2 | 54 | 175 |
| Anisole | 4-Anisoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 70 | 176a |
| Phenetole | 4-Ethoxybenzoyl | Phenetole | 9-11 | 172 |
| Phenetole | 4-Ethoxybenzoyl | CS_2 | 61 | 256 |
| Phenetole | 4-Ethoxybenzoyl | CS_2 | 62 | 72 |
| Phenetole | 4-Ethoxybenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 60 | 176a |
| <i>β</i> -Phenoxyethoxyethyl chloride | (<i>β</i> -Chloroethoxyethoxy)benzoyl | CS_2 | — | 257 |
| <i>o</i> -Cresyl methyl ether | 2-Methyl-4-methoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 100 | 175 |
| <i>m</i> -Cresyl methyl ether | 2-Methyl-4-methoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 92 | 175 |
| <i>m</i> -Cresyl methyl ether | 2-Methyl-4-methoxybenzoyl | CS_2 | — | 245 |
| <i>p</i> -Cresyl methyl ether | 2-Methoxy-5-methylbenzoyl | CS_2 | 70 | 175 |
| <i>p</i> -Cresyl methyl ether | 2-Methoxy-5-methylbenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 82 | 176 |
| 2,4-Dimethylanisole | 2-Methoxy-3,5-dimethylbenzoyl | Ligroin | 8.8 | 245 |
| 2,5-Dimethylanisole | 4-Methoxy-2,5-dimethylbenzoyl | Ligroin | 23 | 247 |
| Diphenyl ether | 4-Phenoxybenzoyl | CS_2 | 25.5 | 151 |
| 1-Methoxynaphthalene | 4-Methoxy-1-naphthoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 85 | 253 |
| 2-Methoxynaphthalene | 2-Methoxy-1-naphthoyl ‡ | $\text{C}_6\text{H}_5\text{NO}_2$ | 80 | 253 |
| Veratrole | 3,4-Dimethoxybenzoyl | CS_2 | 45 | 175 |
| Veratrole | 3,4-Dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | 50 | 175 |
| Benzoin dimethyl ether | 2,4-Dimethoxybenzylsuccinic anhydride, | | 40 | |
| | 2,4-dimethoxybenzylsuccinic acid, | | 4 | |
| | 2,4-dimethoxybenzoylacrylic acid, | CS_2 | 4.6 | 182 |
| | α -(2,4-dimethoxybenzyl)- β -(2,4-dimethoxybenzoyl)propionic acid | | | |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | $\text{C}_6\text{H}_5\text{NO}_2$ | — | 175 |
| Hydroquinone dimethyl ether | 2,5-Dimethoxybenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 11 | 175a |
| Phenol | α -(<i>p</i> -Hydroxybenzyl)- β -(<i>p</i> -hydroxybenzoyl)propionic acid † | Benzene | 25 | 177 |
| Phenol | 4-Hydroxybenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 4 | 176a |
| <i>m</i> -Cresol | 2-Methyl-4-hydroxybenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 25 | 175a |
| <i>p</i> -Cresol | 2-Hydroxy-5-methylbenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 25 | 175a |
| 3-Methyl-5-isopropylphenol | 2-Methyl-4-hydroxy-5-isopropylbenzoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 13 | 175a |
| Thiophene | 2-Thienoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 24 | 175a |
| 2-Chlorothiophene | 5-Chloro-2-thienoyl | $\text{CHCl}_3\text{-CHCl}_2$ | 53 | 175a |
| Acetanilide | 4-Acetaminobenzoyl | CS_2 | 55 | 175a |

* References 217-255 are on pp. 258-259.

† No proof for the position of attachment of the side chain was given.

‡ The acid was not obtained in analytically pure form.

§ The structure of this acid was established by Papa, Schwab, Vitari, and Klingenberg, ref. 176a.

TABLE XV
REACTIONS OF SUBSTITUTED MALEIC ANHYDRIDES

| Aromatic Compound | Product β -Acrylic Acid | Solvent | Yield % | Reference * |
|--------------------------------------|--|-------------------|---------------|-------------|
| <i>A. Methylmaleic Anhydride</i> | | | | |
| Benzene | β -Methyl- β -benzoyl | Benzene | — | 2 |
| Benzene | α -Methyl- β -benzoyl | Benzene | 20 | 177 |
| Benzene | α -Methyl- β -benzoyl | Benzene | 0.71 | 123 |
| | β -methyl- β -benzoyl | | 0.48 | |
| Toluene | α -Methyl- β -p-tolyl | Toluene | 14 | 123 |
| | β -methyl- β -p-tolyl | | — | |
| Mesitylene | <i>trans</i> - β -(2,4,6-Trimethylbenzoyl)- β -methyl- acrylic acid | CS ₂ | 36 | 167 |
| Bromobenzene | <i>cis</i> - β -(4-Bromobenzoyl)crotonic acid, | CS ₂ | 47 | 167, 269 |
| | <i>trans</i> - α -methyl- β -(4-bromobenzoyl)acrylic acid | | 2 | |
| <i>B. Dimethylmaleic Anhydride †</i> | | | | |
| Benzene | <i>cis</i> - α,β -Dimethylbenzoyl | CS ₂ ‡ | 49 | 168 |
| Mesitylene | <i>trans</i> - α,β -Dimethyl- β -(2,4,6-trimethylbenzoyl) | CS ₂ | 61.5 | 168 |
| Diphenyl | <i>cis</i> - α,β -Dimethyl- β -4-phenylbenzoyl | CS ₂ | 50 | 169 |
| Bromobenzene † | <i>cis</i> - α,β -Dimethyl- β -4-bromobenzoyl | CS ₂ | 40 | 169 |
| <i>C. Bromomaleic Anhydride</i> | | | | |
| Benzene | α -Bromo- β -benzoyl, β -bromo- β -benzoyl | Benzene | 31.5 8.5 | 153 |
| <i>D. Dibromomaleic Anhydride</i> | | | | |
| Benzene | <i>cis</i> - α,β -Dibromo- β -benzoyl | CS ₂ | 63 | 166 |
| Mesitylene | <i>cis</i> - α,β -Dibromo- β -(2,4,6-trimethylbenzoyl) | CS ₂ | 79 | 166 |

* References 217-296 are on pp. 288-289.

† Methylpropylmaleic anhydride is reported to give very poor results in the condensation with aromatic compounds. Diphenylmaleic anhydride is reported not to react at all. See ref. 179.

‡ This reaction proceeds better in carbon disulfide than in benzene.

§ Aluminum bromide was used instead of aluminum chloride.

|| The total yield of the mixture was 51%.

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CHAPTER 6

THE GATTERMANN-KOCH REACTION

NATHAN N. CROUNSE *

The Hilton-Davis Chemical Company

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INTRODUCTION

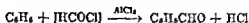
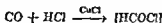
The introduction of an aldehyde group into certain aromatic nuclei by means of carbon monoxide, hydrogen chloride, and an appropriate catalyst is known as the Gattermann-Koch reaction. The catalyst commonly used is aluminum chloride with cuprous chloride as a carrier. The carrier is not necessary when high pressures are used. The reaction was first reported in 1897¹ and was discussed in detail a few years

* Present address, Institute of Medical Research, The Christ Hospital, Cincinnati, Ohio.

¹ Gattermann and Koch, *Ber.*, 30, 1622 (1897).

later.² It has received little attention as a subject of academic study, but its application in the industrial field has been investigated.

Gattermann discovered the reaction while attempting to extend the Friedel-Crafts reaction to the hypothetical formyl chloride. He pictured carbon monoxide as reacting with hydrogen chloride to yield formyl chloride which then condensed with benzene in the presence of aluminum chloride in the same manner as other acid chlorides. The cuprous chloride presumably serves to catalyze the formation of the formyl chloride.



Gattermann did not isolate any intermediate compounds, and little evidence has since been offered to support Gattermann's proposed mechanisms. Hopff and co-workers³ have described a complex compound, $\text{HCOCI} \cdot \text{AlCl}_3 \cdot \text{CuCl}$, formed by the reaction of aluminum chloride, cuprous chloride, hydrogen chloride, and carbon monoxide at 100 atmospheres. This complex reacts with toluene to give an unreported yield of *p*-tolualdehyde. However, the complex is not necessarily an intermediate in all Gattermann-Koch reactions, since formylation can be effected at high pressures without cuprous chloride.

SCOPE AND LIMITATIONS

The chief use of the Gattermann-Koch reaction appears to be the preparation in one step of benzaldehyde and the monoalkyl- and polyalkyl-benzaldehydes. The alkyl group in monoalkylbenzenes directs the aldehyde group almost exclusively to the *para* position.

Benzene furnishes benzaldehyde in yields up to 90%.⁴ Among the monoalkylbenzenes, toluene, ethylbenzene,⁵ *tert*-butylbenzene, *tert*-amylbenzene, cyclohexylbenzene, and (3-methylcyclohexyl)benzene have been converted to the corresponding *p*-alkylbenzaldehydes.⁶ The only yields reported are 85% for *p*-tolualdehyde^{4,6} and 15% for *p*-cyclohexylbenzaldehyde.⁷ The formylation of isopropylbenzene is always accompanied by side reactions. Formylation at atmospheric pressure furnishes an unspecified yield of *p*-isopropylbenzaldehyde,⁸ 2,4-diisopropylbenzal-

² Gattermann *Ann.*, **347**, 347 (1906).

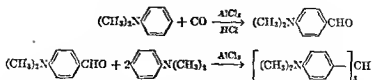
³ Hopff, Nenitzescu, Isacoveu, and Cantunari, *Ber.*, **69**, 2344 (1936).

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Phenol and phenol ethers could not be successfully formylated at atmospheric pressure in benzene as a solvent. This failure to react was attributed to the insolubility of the cuprous chloride in the reaction mixture.¹⁵ It appears probable that formylation at high pressures where cuprous chloride is unnecessary might be successful.

Since nitrobenzene may be used as a solvent for formylation reactions,⁴ it may be concluded that in general *meta*-directing groups in the benzene ring prevent substitution in the nucleus in which they are substituents.

Biphenyl is converted to *p*-phenylbenzaldehyde.^{5, 16} Hydrindene gives a 25% yield of the 5-aldehyde,² and a diisopropyl- α -tetrahydronaphthalene furnishes a diisopropyl- α -tetrahydronaphthaldehyde;⁸ these are the only fused-ring compounds reported to undergo formylation. Naphthalene does not give naphthaldehyde.¹⁷

The synthesis of heterocyclic aldehydes by the Gattermann-Koch procedure has received almost no study. It has been reported that thiophene¹⁸ decomposes during the course of the reaction and that only sufficient thiophene-2-aldehyde to be detected by odor is formed.

The reaction has been extended to the aliphatic and alicyclic series.¹⁹ Cyclohexane yields 1-methyl-2-cyclohexanone under high-pressure formylation. The aliphatic hydrocarbons give ketones, and such reactions have proved to have practical application. Their discussion is beyond the scope of this chapter.

EXPERIMENTAL CONDITIONS

The most important variables in the Gattermann-Koch reaction are the condition and quantity of the catalyst, the carriers, the concentration of the hydrocarbons in the solvent, the pressure, and the temperature.

Catalysts. Anhydrous aluminum chloride has been the catalyst most commonly employed. Aluminum bromide,²⁰ however, was more success-

¹⁵ Gattermann, *Ber.*, **31**, 1149 (1898).

¹⁶ Hey, *J. Chem. Soc.*, 1931, 2476.

¹⁷ Dewar and Jones, *J. Chem. Soc.*, **83**, 212 (1904).

¹⁸ Barger and Easson, *J. Chem. Soc.*, 1933, 2160.

¹⁹ Hopff, *Ber.*, **64**, 2739 (1931); *Ber.*, **65**, 482 (1932); Ger. pat. 512,718 [*C.A.*, **25**, 1258 (1931)]; Ger. pat. 520,154 [*C.A.*, **25**, 3664 (1931)].

²⁰ Reformatsky, *J. Russ. Phys. Chem. Soc.*, **33**, 151 (1901) [*J. Chem. Soc. Abs.*, **80** (D), 327 (1901)].

ful in the formylation of benzene at atmospheric pressure than aluminum chloride, although the latter is satisfactory at high pressures.²¹ Some reports in the literature indicate that pretreatment of the aluminum chloride with moisture is advantageous when using high pressures. There is an optimum amount of water which must be added for satisfactory yields of benzaldehyde from benzene under specified conditions.^{21,22} Exposure of aluminum chloride to moist air gives a very active catalyst.⁹

The amount of catalyst is an important factor. Usually a mole of aluminum chloride is used for each mole of hydrocarbon to be formylated. The ratio of aluminum chloride to benzene was studied carefully in the synthesis of benzaldehyde from benzene at different temperatures using a pressure of 1000 lb. per sq. in. and a reaction period of two hours.²¹ In Table I are shown the results obtained at 25°, 35°, and 50° with changes in the molar ratio of aluminum chloride to benzene.

TABLE I
EFFECT OF QUANTITY OF CATALYST ON YIELD OF BENZALDEHYDE

| Molar Ratio $\frac{\text{AlCl}_3}{\text{C}_6\text{H}_6}$ | Yield of Benzaldehyde % | |
|---|----------------------------------|----------------------------------|
| | Based on Benzene Converted | Based on Aluminum Chloride |
| | At 25° | |
| 0.3 | 20.6 | 68.7 |
| 0.5 | 31.5 | 63.0 |
| 0.75 | 48.6 | 64.8 |
| 1.0 | 65.4 | 65.4 |
| | At 35° | |
| 0.3 | 20.5 | 68.3 |
| 0.5 | 33.8 | 67.6 |
| 0.75 | 39.9 | 53.2 |
| | At 50° | |
| 0.3 | 18.6 | 61.9 |
| 0.5 | 33.0 | 66.0 |
| 0.75 | 39.4 | 52.5 |

²¹ Holloway and Krase, *Ind. Eng. Chem.*, **25**, 497 (1933).

²² Olson, U. S. pat. 1,935,914 [*C.A.*, **28**, 778 (1934)].

It was observed also that too much aluminum chloride in the reaction between isopropylbenzene and carbon monoxide gave decreased yields of *p*-isopropylbenzaldehyde though more hydrocarbon was consumed.⁹ Excess aluminum chloride not only may convert aldehyde to the hydrocarbon and carbon monoxide but it also catalyzes the condensation of carbon monoxide and the hydrocarbon to anthracene and triphenylmethane derivatives.²² It has been demonstrated by using tagged aldehydes that the aryl group holding the aldehyde does not become one of the aryl groups in the anthracene or triphenylmethane by-product.

An industrial grade of aluminum chloride may be employed as catalyst. Its chief impurity is ferric chloride. Aluminum chloride containing titanium chloride as an impurity has been described as a valuable catalyst.¹³ There are no statements in the literature which report any advantage in using highly purified aluminum chloride. A small amount of the preformed complex from aluminum chloride and the desired aldehyde is suggested as a promoter²⁴ and has proved successful in the synthesis of benzaldehyde.²⁵

Carriers. When the Gattermann-Koch reaction is carried out at atmospheric pressure, a carrier is necessary.^{4,5} The function is probably the acceleration of the reaction of carbon monoxide with hydrogen chloride. Cuprous chloride was the first such carrier discovered. Carbon monoxide is known to form a complex with cuprous chloride suitable for gas analysis in acid solution.²⁶ In anhydrous form this complex dissociates readily²⁶ but is more stable as the hydrate $\text{CuCl} \cdot \text{CO} \cdot 2\text{H}_2\text{O}$. The high rate of dissociation at atmospheric pressure may explain in part the slow rate of formylation as compared with that at high pressures.

Titanium tetrachloride¹³ and nickelous chloride²⁷ have been reported to be almost as effective as cuprous chloride. Less efficient are cobaltous chloride, tungsten hexachloride, and ferric chloride.²⁷ Thus from 30 g. of toluene, 45 g. of aluminum chloride, and 2 g. of nickelous chloride a 54% yield of *p*-tolualdehyde resulted which is comparable to that obtained with cuprous chloride. 2,4,6-Trimethylbenzaldehyde was made from mesitylene in a similar manner. With ferric chloride as a carrier, only 14% yield of tolualdehyde was obtained from toluene; with tungsten hexachloride, the yield was only 5%, and with cobaltous chloride it was still lower.

⁹ Hey, *J. Chem. Soc.*, 1935, 72.

¹³ Larson, U. S. pat. 1,989,700 [C.A., 29, 1834 (1935)].

²² Snell and Bifen, *Commercial Methods of Analysis*, p. 609, McGraw-Hill, New York, 1944.

²⁴ Manchot and Friend, *Ann.*, 359, 100 (1908).

²⁷ Koreszynski and Mrosinski, *Bull. soc. chim. France*, [4] 29, 459 (1921).

Concentration of the Hydrocarbon. Ordinarily the aromatic compound to be formylated is diluted with benzene, especially when the compound is an alkylbenzene with a labile alkyl group. Usually a ratio of benzene to aromatic compound of between 2 and 3 to 1 is satisfactory. The benzene inhibits the formation of dialkylbenzenes and thus lowers the amount of dialkylbenzaldehyde obtained as a by-product.

Pressure. Much of the work on the Gattermann-Koch reaction has been carried out at atmospheric pressure. Under these conditions the reaction mixture must be saturated with hydrogen chloride and kept so at all times by continual addition of the gas. At high pressures in an autoclave this is unnecessary. High pressures also increase the rate of absorption of carbon monoxide and increase the yield of product. The higher pressure apparently does not increase appreciably the rate of the transalkylation reaction but increases that of the formylation reaction. Carriers such as cuprous chloride are not necessary when working at high pressure,^{9,21} since benzene and isopropylbenzene have been successfully formylated without them. In the formylation of chlorobenzene and benzene,¹² it is claimed that the addition of titanium chloride is advantageous.

A pressure of 500 lb. per sq. in. has been suggested as satisfactory for formylation of isopropylbenzene.⁹ In the formylation of benzene²¹ a pressure of 1000 lb. per sq. in. was generally used although a pressure as low as 300 lb. was not appreciably less effective. As the pressure is increased from 700 lb. to 1000 lb., the yields gradually reach a constant value asymptotically.

Usually twice the length of time is required for completion of a formylation at atmospheric pressure as compared with high pressure (six or seven hours *versus* three or four).

Temperature. A temperature of 25–35° in formylations under pressure is often adequate,⁹ although 50–60° has been found useful in certain reactions.^{5,12} Higher temperatures with a fixed ratio of aluminum chloride affected the yield of benzaldehyde from benzene unfavorably when the reactions were run beyond an optimum time;²¹ tarry residues containing anthracene and triphenylmethane derivatives increased in quantity.²² At atmospheric pressure a temperature range of 35–40° has been commonly employed.

Reagents and Apparatus. Since the Gattermann-Koch reaction involves two solids, two gases, and a liquid, good agitation is necessary whether operating at high or atmospheric pressure.

Carbon monoxide may be formed by the action of concentrated sulfuric acid upon formic acid. For high-pressure work it is convenient to use the gas obtained in cylinders under 800 lb. pressure.

In reactions at atmospheric pressure the hydrogen chloride, generated as used or from a cylinder, and the carbon monoxide may be combined and introduced into the reaction mixture through a common gas inlet. A convenient apparatus for this purpose has been described by Coleman and Craig.²⁵ More recently a procedure for simultaneous preparation of carbon monoxide and hydrogen chloride has been discovered.²⁶ This consists in the reaction of chlorosulfonic acid with formic acid. It was



found advantageous to add a volume of 100% sulfuric acid equal to that of the chlorosulfonic acid in order to reduce the vigor of the reaction. By employing an amount of chlorosulfonic acid adequate to neutralize 15% of water, commercial 85% formic acid may be substituted for anhydrous formic acid.

When working under high pressure, the reaction mixture is saturated with hydrogen chloride and placed in the autoclave before it is sealed. The carbon monoxide is then introduced.

The addition of nickel carbonyl to a mixture of the aromatic compound, aluminum chloride, and hydrogen chloride has served as a source of carbon monoxide in the formylation of benzene, toluene, xylene, and mesitylene.¹⁷ The yields, however, are lower than in the usual method, and anthracene compounds appear to be formed in significant amounts.

If the reaction is carried out at atmospheric pressure, the reactor consists of a glass vessel fitted with an agitator, a gas inlet extending as near to the bottom of the flask or jar as possible, a thermometer, and an exit tube fitted as a bubble counter.²⁵

For high-pressure work the catalytic hydrogenation rocking autoclave sold by the American Instrument Company has been satisfactory.⁹ The autoclave should be lead lined to prevent corrosion.^{9,21} Copper has been reported to be satisfactory as a liner.²⁰ The use of an iron autoclave has been reported,²⁶ but the possibility of corrosion is a known risk. None of these metals has any known adverse effect on the reaction.

EXPERIMENTAL PROCEDURES

***p*-Tolualdehyde.** (Atmospheric pressure, independent generation of carbon monoxide and hydrogen chloride, cuprous chloride carrier.) This preparation has been described in detail by Coleman and Craig in *Organic Syntheses*.²⁵

²⁵ Coleman and Craig, *Org. Syntheses, Coll. Vol. 2*, 583 (1943).

²⁶ Bert, *Compt. rend.*, **221**, 77 (1945).

²⁰ Hoff, U. S. pat. 1,976,682 [*C.A.*, **28**, 7263 (1934)].

p-Phenylbenzaldehyde.¹⁶ (Atmospheric pressure, cuprous chloride carrier.) A stream of dry carbon monoxide and hydrogen chloride is passed for eight hours into a well-stirred solution of 60 g. of biphenyl in 240 ml. of dry benzene containing 90 g. of anhydrous aluminum chloride and 12 g. of cuprous chloride at 35–40°. After standing overnight the dark-colored semi-solid product is poured on ice. A yellow oil separates. The mixture is steam-distilled to remove benzene and unchanged biphenyl. The residue is extracted with ether, the extract is washed with dilute hydrochloric acid and with water, and the ether is evaporated. The semi-solid residue thus obtained is shaken with an excess of a saturated solution of sodium bisulfite, and after twelve hours the brown bisulfite compound is filtered, washed with ethanol and with ether, and warmed with aqueous sodium carbonate. The aldehyde is then collected, dried on a porous plate, and crystallized twice from petroleum ether (b.p. 80–100°). The yield of pale yellow plates, m.p. 60°, is 52 g. (73%).

p-Isopropylbenzaldehyde.^{2,*} (High pressure, no carrier.) A mixture of 210 g. (1.75 moles) of isopropylbenzene and 315 g. (±0.5 moles) of benzene is saturated with hydrogen chloride and placed in a lead-lined rocking autoclave. Then 255 g. (1.92 moles) of aluminum chloride, which has been ground to 20 mesh, placed in a 1-in. layer in a shallow porcelain dish, and raked every fifteen minutes for two hours to induce hydration, is added. After the air in the autoclave is displaced with carbon monoxide, carbon monoxide is added until the pressure is 500 lb. per sq. in. The pressure is allowed to drop to 300 lb. per sq. in. The carbon monoxide pressure is returned to 500 lb. per sq. in., and the process is repeated until there is no pressure drop. The time of absorption is two and one-half hours, after which the reaction is allowed to proceed for another hour. The temperature of the reaction is 25–30°.

The reaction mixture is hydrolyzed by pouring it onto 2.5 kg. of ice acidified with 5 ml. of concentrated hydrochloric acid. The lower water layer is removed, and the oily layer is washed with 500 ml. of water and then with 500 ml. of 5% aqueous sodium carbonate solution. It is filtered to break the emulsion. After the lower alkaline layer has separated, the oily layer is washed twice with 500-ml. portions of water.

The oil is charged into a round-bottomed flask headed by a 36-in. fractionating column packed with glass helices. Most of the benzene is collected at atmospheric pressure. When the temperature of the liquid in the distilling flask reaches 131°, the flask is cooled to room temperature and the distillation is continued under a vacuum of 135 mm. This permits recovery of 40.5 g. of isopropylbenzene (b.p. 95°/135 mm.).

* The description of this procedure in ref. 9 is a condensed version.

The system is cooled, and the vacuum is lowered to 35 mm. The next fraction consists of 11 g. of benzaldehyde (b.p. 83–88°/35 mm.) contaminated with a small amount of isopropylbenzene. On further distillation at this pressure, 126 g. of *p*-isopropylbenzaldehyde (b.p. 131–133°/35 mm.) is obtained, a yield of 60% based on the aluminum chloride and the unrecovered isopropylbenzene. The yield of 2,4-diisopropylbenzaldehyde (b.p. 151–152°/35 mm.) obtained on further distillation is 25 g. A residue of about 25 g. remains.

Generation of Carbon Monoxide and Hydrogen Chloride from Formic Acid and Chlorosulfonic Acid. An Erlenmeyer flask of suitable capacity is fitted with a two-holed rubber stopper. In one opening is placed a tube to lead off the generated gases; in the other is inserted a dropping funnel whose tip has been drawn to a capillary and whose over-all length permits the tip to be near the bottom of the flask. The dry generator is charged with the desired amount of technical 96–98% formic acid. Chlorosulfonic acid is placed in the dry dropping funnel and allowed to fill the capillary. The flow of chlorosulfonic acid into the formic acid is regulated by the rate of escape of the resulting gases. The rate of evolution of the gases can be increased or decreased by raising or lowering the temperature of the generating flask. The gases produced are anhydrous, and, therefore, no drying towers are needed.

When commercial 85% formic acid is used, the above apparatus is changed by the addition of a pressure equalizer between the top of the dropping funnel and the outlet tube, as shown for the hydrogen chloride generator of Fieser.³¹ The 85% formic acid is placed in the dropping funnel and added through the capillary to a mixture of equal volumes of 100% sulfuric acid and chlorosulfonic acid. No drying towers are necessary.

In Table II are listed all the examples of the Gattermann-Koch reaction that have been found in the literature through 1946.

³¹ Fieser, *Experiments in Organic Chemistry*, p. 394, D. C. Heath and Co., New York 1941.

TABLE II
COMPOUNDS PREPARED BY THE GATTERMANN-KOCH REACTION

| Starting Material | Product | Yield % | Pressure | | Reference |
|--|---|------------|----------|-------------|------------|
| | | | High | Atmospheric | |
| Benzene | Benzaldehyde | 65 | + | | 21 |
| | Benzaldehyde | 85 | + | | 6 |
| | Benzaldehyde | 90* | | + | 4 |
| | Benzaldehyde | — | + | | 22, 24, 35 |
| | Benzaldehyde | — | | + | 20 |
| Toluene | Benzaldehyde | 25† | | + | 17 |
| | p-Tolualdehyde | 85 | + | | 6 |
| | p-Tolualdehyde | 85* | | + | 4 |
| | p-Tolualdehyde | — | | + | 1, 32 |
| | p-Tolualdehyde | 55 | | + | 2 |
| | p-Tolualdehyde | 16† | | + | 17 |
| | p-Tolualdehyde | 46 | | + | 28 |
| | p-Tolualdehyde | 54‡ | | + | 27 |
| Ethylbenzene | p-Ethylbenzaldehyde | — | | + | 1 |
| Chlorobenzene | p-Chlorobenzaldehyde | 70* | | + | 4 |
| | p-Chlorobenzaldehyde | — | | | 6, 13 |
| tert-Butylbenzene | p-tert-Butylbenzaldehyde | — | + | | 5 |
| Isopropylbenzene | p-Isopropylbenzaldehyde | 69 | + | | 9 |
| | p-Isopropylbenzaldehyde | — | | + | 2 |
| | p-Isopropylbenzaldehyde | — | + | | 33 |
| | 2,4-Diisopropylbenzaldehyde | — | + | | 9, 33 |
| | 2,4-Diisopropylbenzaldehyde | — | | + | 8 |
| tert-Amylbenzene | p-tert-Amylbenzaldehyde | — | + | | 5 |
| Cyclohexylbenzene | p-Cyclohexylbenzaldehyde | — | + | | 5 |
| | p-Cyclohexylbenzaldehyde | 14-16 | | + | 7 |
| (3-Methylcyclohexyl)benzene | p-(3-Methylcyclohexyl)benzaldehyde | — | + | | 5 |
| m-Xylene | 2,4-Dimethylbenzaldehyde | 46 | | + | 2 |
| | 2,4-Dimethylbenzaldehyde | 20† | | + | 17 |
| | 2,4-Dimethylbenzaldehyde | — | | + | 1, 32 |
| o-Xylene | 3,4-Dimethylbenzaldehyde | — | | + | 1, 32 |
| | 3,4-Dimethylbenzaldehyde | 58 | | + | 2 |
| p-Xylene | 2,4-Dimethylbenzaldehyde | — | | + | 1 |
| | 2,4-Dimethylbenzaldehyde | 45 | | + | 2 |
| Diisopropylbenzene | Diisopropylbenzaldehyde ‡ | — | | + | 8 |
| p-Cymene | Diisopropylmethylbenzaldehyde ‡ | — | + | | 8 |
| Diisopropyltoluene | Diisopropylmethylbenzaldehyde ‡ | — | + | | 8 |
| Diisopropyl- <i>α</i> -tetrahydronaphthalene | Diisopropyl- <i>α</i> -tetrahydronaphthaldehyde ‡ | — | + | | 8 |
| Diisopropylstyrene | Diisopropyl- <i>α</i> -methylbenzaldehyde ‡ | — | + | | 8 |
| Pseudocumene | 2,4,5-Trimethylbenzaldehyde | 56 | | + | 2 |
| Mesitylene | 2,4,5-Trimethylbenzaldehyde | — | | + | 34 |
| | 2,4,6-Trimethylbenzaldehyde | 80 | | + | 2 |
| | 2,4,6-Trimethylbenzaldehyde | — | | + | 1, 32 |
| | 2,4,6-Trimethylbenzaldehyde † | — | | + | 17 |
| | 2,4,6-Trimethylbenzaldehyde ‡ | — | | + | 27 |
| Biphenyl | p-Phenylbenzaldehyde | 30 | | + | 2 |
| | p-Phenylbenzaldehyde | 73 | | + | 16 |
| Hydrindene | 5-Hydrindenaldehyde | 25 | | + | 2 |
| Thiophene | 2-Thiophenaldehyde | Negligible | | + | 18 |
| Cyclohexane | 1-Methyl-2-cyclohexanones | — | + | | 19 |
| Dimethylaniline | Crystal violet leuco base | — | + | | 14 |
| Triisopropylbenzene | Diisopropylbenzaldehyde ‡ | — | + | | 8 |

* Nitrobenzene was used as solvent.

† Nickel carbonyl was used as the source of carbon monoxide.

‡ Nickelous chloride was used as catalyst.

§ Orientation unknown.

²² Farbenfabriken vorm. Friedr. Bayer, Ger. pat. 93,706 [*Frds.*, 5, 97 (1897-1900)].

²³ Meuly, U. S. pats. 2,158,518-9 (*Chem. Zentr.*, 1938, I, 3388).

²⁴ John, Gunther, and Rathmann, *Z. physiol. Chem.*, 268, 104 (1941).

²⁵ Denman, Krebs, and Borchers, *Tech. Mitt. Krupp Tech.*, 6, 59 (1938) [*C.A.*, 33, 6257 (1939)].

CHAPTER 7

THE LEUCKART REACTION

MAURICE L. MOORE

Smith, Kline and French Laboratories

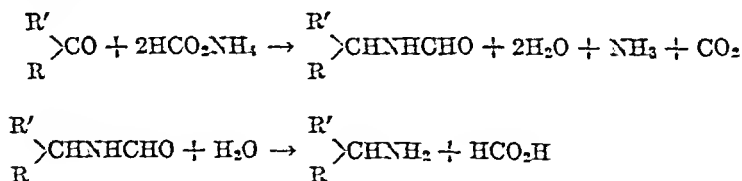
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INTRODUCTION

The Leuckart reaction is a process for the reductive alkylation of ammonia or primary or secondary amines by certain aldehydes and ketones. It is distinguished by the fact that the reduction is accomplished by formic acid or a derivative of formic acid and should be compared with the reductive alkylation using hydrogen discussed in Chapter 3 of Volume IV of *Organic Reactions*. The reaction is carried out by heating a mixture of the carbonyl compound and the formic acid salt or formyl derivative of ammonia or the amine. Primary and secondary amines produced in the reaction often are obtained as the formyl derivatives and must be recovered by hydrolysis; tertiary amines are obtained as the formates. The reaction may be illustrated by the following equations.



Leuckart¹ discovered the reaction in an attempt to prepare benzylidenediformamide, $\text{C}_6\text{H}_5\text{CH}(\text{NHCHO})_2$, by heating benzaldehyde with formamide in an experiment patterned after the preparation by Roth² of the corresponding acetamide derivative. The reaction with formamide was found to take a different course, leading to benzylamine and its formyl derivative, dibenzylamine and its formyl derivative, and tribenzylamine. Ammonium formate was found to react in the same

¹Leuckart and co-workers, *Ber.*, **18**, 2341 (1885); **19**, 2128 (1886); **20**, 104 (1887); **22**, 1409, 1851 (1889).

²Roth, *Ann. Chem. Pharm.*, **154**, 72 (1870).

way as the amide, and benzophenone could be converted to benzo-hydrylamine by the use of conditions somewhat more drastic than those required with benzaldehyde. Leuckart's experiments with aliphatic aldehydes and ketones were not extensive,³ but Wallach⁴ and Kijner⁵ applied the reaction to many such compounds. The method received little attention from other investigators until Ingersoll and his associates⁶ reviewed the subject and applied the reaction to the synthesis of a series of substituted α -phenethylamines; since the appearance of this work the method has been employed extensively. Among the better-known modifications of the process are the preparation of trimethylamine⁷ from ammonia, formaldehyde, and formic acid and the Eschweiler-Clarke^{8,9} procedure for the methylation of primary and secondary amines by the aid of formaldehyde and formic acid.

MECHANISM OF THE REACTION

A single mechanism capable of accounting for all the variations of the Leuckart process can be postulated on the basis of the decomposition of the ammonium salt or of the amide, by thermal or hydrolytic means, respectively, to formic acid and ammonia or an amine. The base so formed may then react with the carbonyl compound to give an addition

product $\left(\begin{array}{c} \diagup \quad \diagdown \\ \text{C} \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{N} \end{array} \right)$ which is reduced by formic acid to an amine $\left(\begin{array}{c} \diagup \quad \diagdown \\ \text{CH} - \text{N} \\ \diagdown \quad \diagup \end{array} \right)$; reaction of this amine with more formic acid leads to

the salt or the amide. These transformations appear to be the only ones concerned in the formation of a tertiary amine from a carbonyl compound and the formate or formyl derivative of a secondary amine, but there are numerous other possible intermediates in the synthesis of primary and secondary amines. For example, the addition product from a carbonyl compound and ammonia or a primary amine may undergo

³ Leuckart, *J. prakt. Chem.*, [2] 41, 330 (1896).

⁴ Wallach and co-workers, (a) *Ber.*, 24, 3992 (1891); (b) *Ann.*, 269, 347 (1892); (c) 272, 100 (1893); (d) 276, 296 (1893); (e) 282, 338 (1896); (f) 300, 293 (1898); (g) 343, 54 (1905).

⁵ Kijner, *J. Russ. Phys. Chem. Soc.*, 31, 877, 1033 (1899); 32, 381 (1900) [*J. Chem. Soc. (Abstr.)*, 78 (5), 277, 333, 629 (1900)].

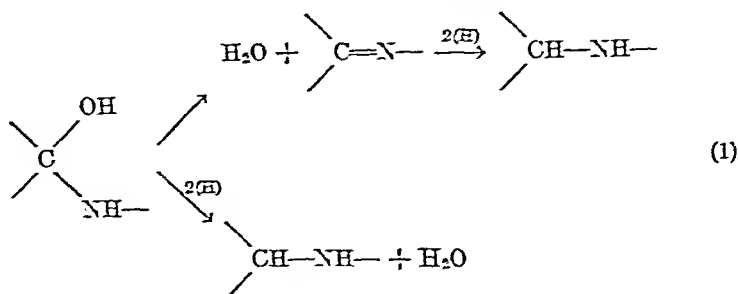
⁶ Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Am. Chem. Soc.*, 53, 1808 (1930).

⁷ Sommelet and Ferrand, *Bull. soc. chim. France*, [4] 35, 446 (1924).

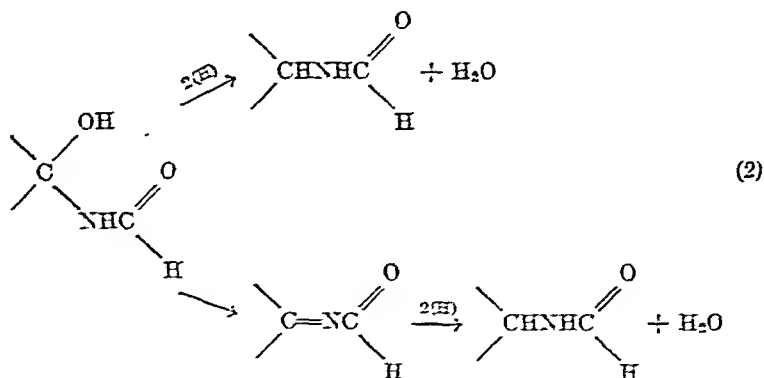
⁸ Eschweiler, *Ber.*, 38, 880 (1905).

⁹ Clarke, Gillespie, and Weissman, *J. Am. Chem. Soc.*, 55, 4571 (1933).

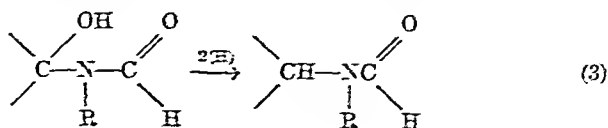
loss of water, and the imine so formed may be the intermediate which is reduced to the amine (equation 1). Furthermore, when formamide is



present in the reaction mixture (either added as such or produced by dehydration of ammonium formate) it may give rise to an addition product capable of reduction directly to the formyl derivative of the primary amine or of dehydration and reduction to the same substance.



If the reacting amide is derived from a primary amine the addition product cannot undergo dehydration but must be reduced directly if it participates in the reaction. The formyl derivative of a secondary

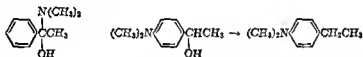


amine (HCONR_2) cannot give an addition product; evidently the first step in its reaction must be hydrolysis.

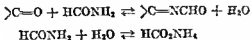
Imines, >C=N- , and addition products from carbonyl compounds

and ammonia or amines, $\text{>C}\begin{array}{c} \text{OH} \\ \diagup \quad \diagdown \\ \text{N} \end{array}$, were suggested in the preceding

paragraphs as intermediates in the Leuckart reaction, intermediates which are reduced by formic acid. Benzalaniline, a representative imine, is reduced almost quantitatively to benzyaniline by heating at 140-160° with triethylammonium formate.¹⁰ No examples are available of the action of formic acid on the addition product of a carbonyl compound and ammonia or an amine; but *p*-dimethylaminophenylmethylcarbinol, a vinylog of the addition product from acetophenone and dimethylamine, is reduced to *p*-dimethylaminoethylbenzene in poor yield by heating at 130-135° with triethylammonium formate.¹¹ Formic acid could not be used in these reductions since it led to the formation of resinous materials.



Much of the study^{6,10,11,12} of the mechanism of the Leuckart process has been concerned with the reactions involved in the formation of primary amines. Inasmuch as the experimental temperature (150° or higher) usually employed is above that at which ammonium formate rapidly generates formamide and water it has been considered that formamide may be the true reagent even in preparations in which ammonium formate is employed. However, acetophenone in diethylene glycol at 120-130° does not react with formamide over a period of fifteen hours, whereas with ammonium formate under the same conditions a 10% yield of α -phenethylamine is obtained in four hours.¹² At the higher temperatures ordinarily used, formamide could furnish ammonium formate in the following way.



In experiments with acetophenone and formamide at 165-173°, the addition of anhydrous calcium sulfate brought down the yield of α -

¹⁰ Alexander and Wildman, *J. Am. Chem. Soc.*, **70**, 1187 (1948).

¹¹ Ingersoll, Brown, Levy, and Haynes, personal communication.

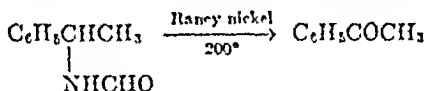
¹² Davies and Rogers, *J. Chem. Soc.*, **1944**, 126.

¹³ Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

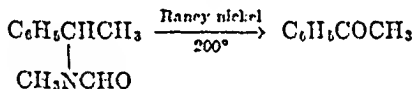
phenethylamine from 30% to 17%.^{12a} The available evidence does not permit one to exclude either of the mechanisms shown in equations 1 and 2 on p. 304; both mechanisms may be operative under appropriate experimental conditions.

The reaction between benzophenone and formamide is catalyzed by ammonium formate, magnesium chloride, or ammonium sulfate, and it has been suggested that the catalyst polarizes the carbonyl group and thus facilitates the addition of formamide or ammonia.^{12a}

Formyl derivatives of primary amines are stable substances, and many of them can be heated to 200° without undergoing any change. When they are heated to this temperature in the presence of Raney nickel, however, they furnish ketones.^{12b} Formyl derivatives of second-



ary amines undergo the same reaction, but the yields of carbonyl compounds are poor.^{12a}



SCOPE OF THE REACTION

The method appears best adapted to aromatic aldehydes and water-insoluble ketones boiling at about 100° or higher. Higher aliphatic ketones, aromatic aldehydes and ketones, and certain terpenoid ketones have been used successfully, with yields of 40–90%. The application of the reaction to aliphatic aldehydes and ketones of lower molecular weight has been very limited. The method is definitely superior to that involving the formation and reduction of aldoximes and ketoximes and has succeeded where the reduction of oximes is unsatisfactory, particularly with compounds in which functional groups are present that are readily attacked by many reducing agents. Thus, the Leuckart method gives an 82% yield of pure α -*p*-chlorophenethylamine from *p*-chloroacetophenone, whereas the reduction of *p*-chloroacetophenone oxime with sodium and ethanol, sodium amalgam and acetic acid, or by catalytic means, proceeds in all instances with extensive removal of the nuclear halogen. *p*-Bromoacetophenone and *m*-nitroacetophenone are readily

^{12a} Webers and Bruce, *J. Am. Chem. Soc.*, **70**, 1422 (1948).

^{12b} Métayer and Mastagli, *Compt. rend.*, **225**, 457 (1947).

converted to the corresponding amines without disturbance of the halogen or nitro group.

The reaction is not limited to ammonium formate or formamide. Methyl formate has been used with a few primary amines. Substituted ammonium formates, such as monomethyl- or dimethyl-ammonium formate, react satisfactorily and lead to the formation of secondary and tertiary amines of mixed type that cannot be obtained easily by other methods. Thus, the N-methyl, N-ethyl, and N-butyl derivatives of α -phenethylamine are prepared in yields of 60-70% by the action of methyl-, ethyl-, and butyl-ammonium formates on acetophenone.^{12,14}

Methylation of Amines with Formaldehyde

The simplest aldehyde, formaldehyde, reacts very readily, and it is difficult to prevent the formation of tertiary amines. Formaldehyde reacts with ammonium formate and formic acid, but trimethylamine is the product isolated in highest yield.⁷ Formaldehyde was first used alone⁸ for the methylation reaction, but Clarke⁹ obtained better yields (80%) by using an excess of formic acid with the formaldehyde. One molecular proportion (or a slight excess) of formaldehyde and two to four molecular proportions of formic acid are used for each methyl group introduced, indicating that it is mainly the formic acid that supplies the hydrogen involved in the reduction. The reaction is carried out on the steam bath. This variant of the Leuckart reaction, as mentioned earlier, is commonly known as the Eschweiler-Clarke procedure.

Ethylamine,⁸ piperazine,⁸ anabasine,¹⁶ the benzylamines,^{8,15,17} phenethylamines,¹⁶ and methoxyphenethylamines¹⁷ react to give almost theoretical yields of the corresponding tertiary amines. Secondary amines react as readily as primary amines to give the corresponding methyl derivatives although N-benzyl-3,4-dimethoxyphenethylamine¹⁷ gives unsatisfactory results, probably owing to partial cyclization.¹⁸ Dibenzylamine gives a 75% yield of the anticipated methyl-dibenzylamine, 6-12% of a more volatile base, probably dimethylbenzylamine, and a similar amount of benzaldehyde.⁸ Further application of the process is illustrated by the complete methylation of ethylenediamine and tetramethylenediamine in yields of 92%.

¹² Novelli, *J. Am. Chem. Soc.*, **61**, 520 (1939).

¹⁴ Busch and Lefhelm, *J. prall. Chem.*, [2] **77**, 21, 23 (1908).

¹⁵ Orechhoff and Norkina, *Ber.*, **65**, 724 (1932).

¹⁶ Decker and Becker, *Ber.*, **45**, 2404 (1912).

¹⁷ Buck and Baltaly, *J. Am. Chem. Soc.*, **62**, 161 (1940), **63**, 1904 (1941); **64**, 2263 (1942).

¹⁸ Buck, *J. Am. Chem. Soc.*, **66**, 1769 (1944).

The reaction fails with compounds in which strongly polar groups are attached to the nitrogen, such as amides, urea, guanidine, and hydroxylamine, as these appear to yield hydroxymethyl derivatives only. Moreover, the reaction cannot be applied successfully to the methylation of aniline, which on warming with formaldehyde and formic acid is converted into condensation products of high molecular weight.¹⁹ On the other hand, it is reported that formaldehyde reacts with *p*-toluidine in an excess of 90% formic acid to give dimethyl-*p*-toluidine,²⁰ and with 2,4,6-tribromoaniline⁹ and mesidine,²¹ in which the active positions in the benzene nucleus are occupied, to form the dimethyl derivatives in 73–77% yields.

Some of the amino acids can be methylated by treatment with formaldehyde and formic acid.⁹ For example, glycine yields 60–70% of dimethylglycine; complex, non-crystalline products as well as volatile bases, mainly trimethylamine, are formed also. α -Aminoisobutyric acid and α -phenyl- α -aminobutyric acid give 70–80% yields of the dimethyl derivatives, but the yield from β -aminopropionic acid is only 38%. However, with alanine none of the dimethyl derivative is isolated and 36% of the nitrogen is converted into methylamines. Similar results are obtained with leucine, glutamic acid, etc., in all of which an even greater proportion of the nitrogen is cleaved from the molecule.

Reactions of Higher Aliphatic Aldehydes

The Eschweiler-Clarke procedure is essentially specific for reactions with formaldehyde. Higher aldehydes usually fail to react or react in different ways at steam-bath temperatures. Thus, a mixture of acetaldehyde, ammonium formate, and formic acid yields no carbon dioxide on heating on the steam bath, and from the resulting bases only 2-methyl-5-ethylpyridine has been isolated.⁹ Acetaldehyde and propionaldehyde give only tars when heated with mesidine or 2,4,6-tribromoaniline in formic acid.²¹ However, a 63% yield of *N,N'*-dibutylpiperazine is obtained²² upon refluxing butyraldehyde with piperazine in formic acid for three hours.

In the Leuckart method, valeraldehyde reacts with ammonium formate to give triamylamine,⁴² with aniline and formic acid to give diamylaniline, and with methylaniline and formic acid to give methylamylaniline.

¹⁹ Wagner, *J. Am. Chem. Soc.*, **55**, 724 (1933).

²⁰ Eisner and Wagner, *J. Am. Chem. Soc.*, **56**, 1938 (1934).

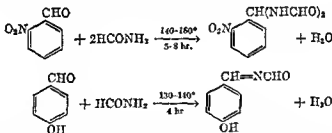
²¹ Emerson, Neumann, and Moundres, *J. Am. Chem. Soc.*, **63**, 972 (1941).

²² Forsee and Pollard, *J. Am. Chem. Soc.*, **57**, 1788 (1935).

Reactions of Aromatic and Heterocyclic Aldehydes

When benzaldehyde is heated with an excess of ammonium formate to a temperature of 180° for several hours, 35–40% of pure tribenzylamine is isolated, along with varying quantities of *N,N*-dibenzylformamide, dibenzylamine, *N*-benzylformamide, and benzylamine.¹ Dibenzylamine and its formyl derivative are obtained in 10–15% yields; only small amounts of the monobenzylamine and its formyl derivative are isolated. Although a portion of the benzaldehyde remains unchanged, as much as 20% is converted into polymerized products. When refluxed for five days with piperazine in formic acid, benzaldehyde gives an 84% yield of *N,N'*-dibenzylpiperazine.²

Substitution in the ring of the aromatic aldehyde tends to reduce the reactivity toward the Leuckart reagents. Although the methoxybenzaldehydes give satisfactory yields of the formyl derivatives of the amines when treated with substituted ammonium formates,³ it has been reported that some substituted benzaldehydes, such as piperonal, 6-nitropiperonal, and the hydroxy, nitro, and alkyl substituted benzaldehydes, are recovered unchanged from the reaction with formamide at 130 – 140° ; in the presence of a trace of pyridine, the nitro and alkyl substituted benzaldehydes condense to give 40–60% of the bisamides, and the hydroxybenzaldehydes give about 65% of the benzalamides.⁴



A 65% yield of the bisamide⁵ is obtained by bubbling dry hydrogen chloride through a suspension of 6-nitroveratraldehyde in formamide for one hour at 45 – 50° .

Furfural is reported to be converted to furfurylamine by reaction with formamide,⁶ although the yield is not indicated and no mention is

¹ Wofahn and Erdelmeier, *Arch. Pharm.*, **280**, 215 (1942).

² Pandya and coworkers, *Proc. Indian Acad. Sci.*, **15A**, 6 (1942) [*C.A.*, **36**, 6144 (1942)]; references to earlier papers on this work are given.

³ Fettscher and Bogert, *J. Org. Chem.*, **4**, 71 (1939).

⁴ Nabenhauer, Abstract of a paper presented at the 93rd meeting of the American Chemical Society, Chapel Hill, North Carolina, April, 1937.

made of the presence of any of the corresponding secondary or tertiary amines. *N*-Methylfurfurylamine,²² *N,N*-dimethyl-, and *N,N*-diethylfurfurylamine^{23,24} are prepared from *N*-methyl-, *N,N*-dimethyl-, and *N,N*-diethyl-formamide.

Reactions of Aliphatic Ketones

Acetone reacts with α -naphthylamine and methyl formate in an autoclave to produce isopropyl- α -naphthylamine.²⁵ Diethyl ketone²⁶ is reported to yield 3-aminopentane acetate by reaction with ammonium formate in the presence of acetic acid, and pinacolone reacts with excess formamide to produce the formyl derivative of methyl-*tert*-butylcarbinamine in a yield of 52%.²⁷ The reaction has also been applied to a variety of methyl alkyl ketones (methyl propyl ketone,¹² methyl butyl ketone,²⁸ methyl amyl ketone,^{13,29} methyl hexyl ketone,^{3,12,30} and methyl cyclohexyl ketone³¹) to give the corresponding primary 2-aminoalkanes in yields of 30–60%. Dipropyl, dibutyl, and diheptyl ketones give yields of 40–80% of the primary amines.

Aliphatic ketones of certain types have been shown to be unsuitable for the reaction because of the formation of resinous by-products. Thus, minimum yields of primary amines are obtained from benzalacetone⁶ or acetylacetone.¹² It appears that the method is unsuitable for application to α,β -unsaturated ketones.

Phenylacetone, substituted phenylacetones,^{31–33} and diphenylacetone³² react to give primary amines in yields ranging from 20% to 70%. Secondary and tertiary amines are prepared in lower yields from these ketones in reactions with mono- or di-substituted amines and formic acid; the time necessary to complete such a reaction is longer.

²² Wellmuenster and Jordon, *J. Am. Chem. Soc.*, **67**, 415 (1945).

²³ Speer, U. S. pat. 2,108,147 [*C.A.*, **32**, 2542 (1938)].

²⁴ Rohrmann and Shonle, *J. Am. Chem. Soc.*, **65**, 1516 (1944).

²⁵ Blicke and Zienty, *J. Am. Chem. Soc.*, **61**, 93 (1939).

²⁶ Johns and Burch, *J. Am. Chem. Soc.*, **60**, 919 (1938).

²⁷ Novelli, *Anales quim. argentina*, **27**, 163 (1933) [*C.A.*, **34**, 1627 (1940)].

²⁸ Bobranskii and Drabik, *J. Applied Chem. U.S.S.R.*, **14**, 410 (1941) [*C.A.*, **35**, 2531 (1942)].

²⁹ Elks and Hey, *J. Chem. Soc.*, **1943**, 15.

³⁰ Suter and Weston, *J. Am. Chem. Soc.*, **63**, 602 (1941); **64**, 533 (1942).

³¹ Sugawara, Kakemi, and Karumi, *Ber.*, **73**, 782 (1940).

³² Kakemi, *J. Pharm. Soc. Japan*, **60**, 11 (1940) [*C.A.*, **34**, 3748 (1940)].

³³ Nabenhauer, U. S. pat. 2,246,529 [*C.A.*, **35**, 6095 (1941)].

³⁴ Rajagopalan, *Proc. Indian Acad. Sci.*, **14A**, 125 (1941) [*C.A.*, **35**, 1603 (1942)].

Reactions of Aliphatic-Aromatic and Aliphatic-Heterocyclic Ketones

The Leuckart reaction has been applied successfully to many aliphatic-aromatic ketones, such as acetophenone,^{4c, 5, 10, 12, 31, 40, 41} propiophenone,^{10, 12} isobutyrophenone,¹⁰ caprophenone,¹² and laurophenone,¹² with yields ranging from 50% to 85%. Acetophenones with a methyl group or halogen in the ring react as readily as the unsubstituted compound; the higher alkyl substituted and nitro derivatives appear to be less reactive, giving yields of 15-25% less even though the condensation time is longer.^{4, 12, 13, 31, 42} Hydroxyl substituted aryl derivatives polymerize so readily in formic acid that the results are unsatisfactory.

α -Acetothienone,⁴³ α -propiothienone,⁴³ β -acetonaphthone,⁶ *p*-phenylacetophenone,⁶ and *p*-phenoxyacetophenone⁶ readily undergo the reaction in 40-85% yields.

Secondary and tertiary amines can be readily prepared from the above aliphatic-aromatic ketones by the use of methyl-, ethyl-, butyl-, dimethyl-, or diethyl-amine, aniline, or naphthylamine in place of ammonia with the formic acid. Yields for the compounds of lower molecular weight are almost as good as with the primary amine, while compounds of higher molecular weight give slightly lower yields, and laurophenone gives no product when heated with dimethylamine and formic acid at 160-180° for twenty-eight hours.¹²

β -Benzoylpropionic acid is reported not to give the corresponding amine.¹⁰

γ -Nitro- β -phenylbutyrophenone is converted to 2,2',4,4'-tetraphenylazadipyrromethine (I) in yields up to 33% by reaction with either ammonium formate or formamide.^{11, 44} The corresponding substituted azamethines can be prepared in comparable yields from γ -nitro- β -(dimethylamino-, hydroxy-, methylenedioxy-, methoxy-, and nitrophenyl)butyrophenones, γ -nitro- β -phenyl-*p*-methoxybutyrophenone, and γ -nitro- β -anisyl-*p*-methoxybutyrophenone. β -Benzoyl- α -phenylpropionitrile also reacts with ammonium formate to give 2,2',4,4'-tetraphenylazadipyrromethine along with a small amount of the formyl derivative of 5-amino-2,4-diphenylpyrrole; if formamide is used instead of ammonium formate the substituted pyrrole becomes the major product (59%), unless the reaction is run for a very long time (seventeen hours), in which event the azamethine again predominates. As might

^{4c} Ingersoll, *Org. Syntheses, Coll. Vol. 2*, 503 (1943).

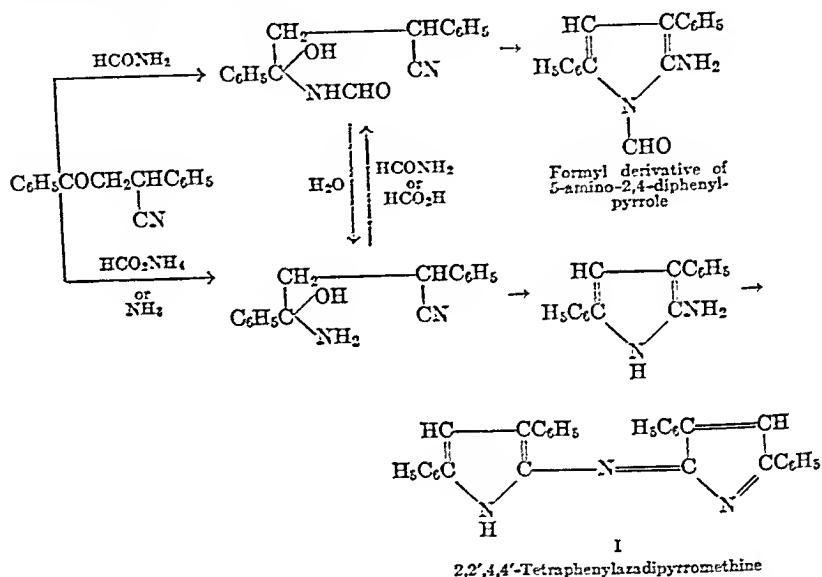
⁴¹ Ott, *Ann.*, 488, 193 (1931).

⁴² Geigy A.-G., Swiss pat. 211,783 [*C.A.*, 36, 4634 (1942)].

⁴³ Blicke and Bueckhalter, *J. Am. Chem. Soc.*, 64, 477 (1942).

⁴⁴ Rogers, *J. Chem. Soc.*, 1943, 590.

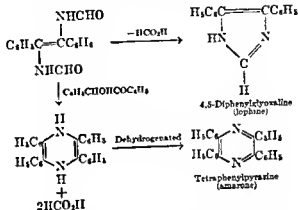
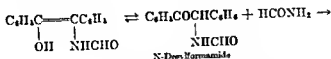
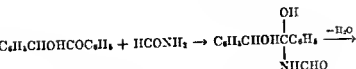
be expected from this observation, treatment of the isolated pyrrole with ammonium formate leads to the formation of the azamethine. A precursor of the pyrrole has been isolated, but, because of the ease with which it is converted into the pyrrole, it has not been identified with certainty. The mechanism of these remarkable reactions has not been elucidated, but the following equations have been suggested to account for the products obtained.



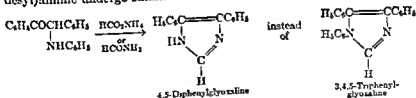
Benzoin behaves abnormally with the Leuckart reagent, giving chiefly glyoxalines along with lesser amounts of diazines. Benzoin reacts with ammonium formate³ at 230° to give tetraphenylpyrazine (amarone) almost quantitatively along with a small amount of 2,4,5-triphenylglyoxaline (lophine). However, a 75% yield of 4,5-diphenylglyoxaline and a 10% yield of tetraphenylpyrazine result from heating the benzoin with formamide at $185\text{--}230^\circ$.⁴⁵ Similar products are obtained from anisoin, benzanisoin, and *p*-toluoin. The mechanism shown on p. 313 has been suggested to account for these products. The addition of acetic anhydride to a reaction mixture of benzoin and formamide leads to the formation of some *N*-desylformamide along with a 36% yield of 4,5-diphenylglyoxaline.⁴⁵ *N*-Desylaniline reacts with ammonium formate

³ Novelli, *Anal. asoc. quim. argentina*, **27**, 161 (1939) [*C.A.*, **34**, 1659 (1940)].

⁴⁵ Davidson, Weiss, and Jelling, *J. Org. Chem.*, **2**, 328 (1937).



to give a 40% yield of 4,5-diphenylglyoxaline instead of the expected 3,4,5-triphenylglyoxaline. N-Desyl-*p*-toluidine and N-(*p,p'*-dimethoxydesyl)aniline undergo similar reactions with formamide.⁶⁷



Reactions of Aromatic Ketones

Benzophenone reacts with 1.5 parts of solid ammonium formate, in a closed tube at 200-220° for four to five hours, to give an excellent yield of formylbenzohydrylamine, which may be hydrolyzed with ethanolic hydrochloric acid.¹ The reaction product is contaminated with some of the secondary amine, dibenzohydrylamine. With ammonia and

⁶⁷ Novelli and Somaglino, *Anal. soc. quim. argentina*, **31**, 147 (1933) [*C.A.*, **33**, 2957 (1944)].

formic acid, an 80% yield of the primary amine is obtained.^{12,43} Fluorenone and benzofluorenone⁴³ give the expected 9-aminofluorenes in yields of 65–75%. Benzoylbenzoic acid¹⁹ yields chiefly an unidentified solid.

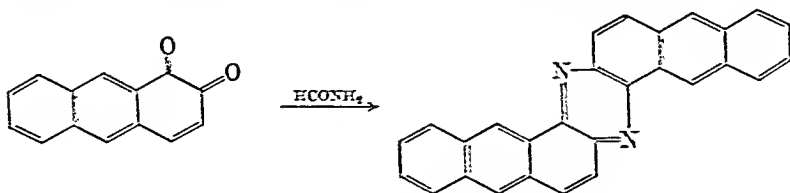
Reactions of Alicyclic Ketones

Cyclohexanone and its derivatives^{4,10,50} have been converted to the corresponding primary amines, accompanied by varying quantities of the secondary amines. With more complicated cyclic ketones, such as camphor,^{4,6,51,52} fenchone,^{4,6} menthones,^{4,10,53} carvomenthones,⁵³ and thujone,^{54,55} the reaction takes place less readily and requires a higher temperature or a longer time. No reaction occurs with menthone at 130° for three to four hours,⁴ whereas an 80% yield of menthylamines is obtained from the reaction at 180–190° for twenty-five hours¹⁰ or at 220–230° for five to six hours. A 20–35% conversion of carvomenthone to carvomenthylamines is obtained after forty-eight hours of refluxing at 130°.⁵³ Bornylamine is obtained in a yield of 55–65% from camphor.^{4,11} Carvone and α -bromocamphor are reported to be converted into neutral resins with only about 10% of the desired amines being isolated.¹⁰

Reactions of Quinones

p-Quinones also undergo the Leuckart reaction;⁴² for example, the diformyl derivative of 9,10-diamino-9,10-dihydroanthracene is produced in the reaction of formamide with 9,10-anthraquinone. The free diamine can be obtained by hydrolysis with alcoholic potassium hydroxide.

o-Quinones, on the other hand, do not react normally but give the corresponding pyrazines. Thus, 1,2-anthraquinone is converted to *bis-ang-dianthracenopyrazine* (anthrazine). Acenaphthoquinone, substi-



⁴² Mettler, Martin, Neracher, and Staub, U. S. pat. 2,276,587 [C.A., 36, 4633 (1942)].
⁴³ Schiedt, *J. prakt. Chem.*, [2] 157, 203 (1941).

⁵⁰ Wegler and Frank, *Ber.*, 70, 1279 (1937).

⁵¹ Wegler and Ruber, *Ber.*, 68, 1055 (1935).

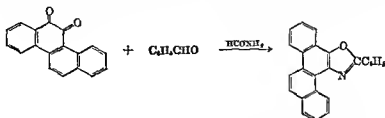
⁵² Tarbell and Paulson, *J. Am. Chem. Soc.*, 64, 2842 (1942).

⁵³ Read et al., *J. Chem. Soc.*, 1926, 2217; 1934, 231.

⁵⁴ Short and Read, *J. Chem. Soc.*, 1938, 2016.

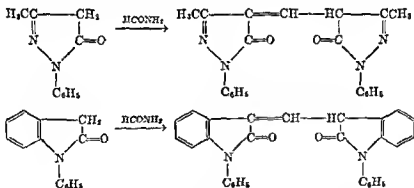
⁵⁵ Dickison and Ingersoll, *J. Am. Chem. Soc.*, 61, 2477 (1939).

tuted acenaphthoquinones, phenanthraquinone, chrysenequinone, etc., undergo similar reactions with formamide. The addition of an aromatic aldehyde to a mixture of formamide with an *o*-quinone leads to the formation of an oxazole; for example, when chrysenequinone is treated with formamide in the presence of benzaldehyde, 2-phenylchrysene-oxazole is isolated.



Reactions of a Pyrazolone and an Oxindole

4,4'-Methyldiylne-bis(1-phenyl-3-methyl-5-pyrazolone) results from the reaction of formamide with 1-phenyl-3-methyl-5-pyrazolone, while methyldiylne-bis(*N*-phenyloxindole) is the product from *N*-phenyloxindole.⁴⁰



SIDE REACTIONS

The normal successive Leuckart reaction or reactions resulting in the formation of the secondary or the tertiary amine have been mentioned above as responsible for by-products in the preparation of primary and secondary amines. Under the influence of the bases present the carbonyl component of the reaction mixture may undergo condensations of the aldol type, some of the products of which may contain carbonyl groups

capable of undergoing the Leuckart reaction. Although such side reactions have not been extensively investigated it is likely that they are concerned in the formation of the resinous by-products sometimes obtained.

EXPERIMENTAL CONDITIONS

The Ammonium Formate or Formamide

Much has been written about the effective reagent in the Leuckart reaction, but no very specific conclusions can be reached. Dry solid ammonium formate was used by Leuckart,¹ and by Wallach in his first experiments,⁴ and the reaction mixture was heated at a temperature of 180–230° in a sealed tube. Later, Wallach obtained better yields by using a mixture of ammonia or substituted amine with formic acid. Formamide was used by Ott⁴¹ and Ingersoll¹⁹ in the preparation of α -phenethylamine from acetophenone. Anhydrous formamide alone is not a satisfactory reagent; the temperature required for the reaction is much higher, the yields are greatly decreased, and the sublimation of ammonium carbonate becomes troublesome. An ammonium formate-formamide reagent prepared by Ingersoll⁶ from commercial ammonium carbonate-carbamate and formic acid gave excellent results in his experiments.

In many instances,^{10,12} the most satisfactory reagent appears to be formamide or ammonium formate supplemented by the addition of sufficient 90% formic acid to maintain a slightly acidic medium and to serve as an active reducing agent. One to three equivalents of formic acid is generally required, and occasional distillation of accumulated water may be necessary to maintain a suitably high reaction temperature. The presence of formic acid appears to diminish the aldol-type side reactions and traps ammonia that otherwise would appear as such or as the carbonate.

Wallach⁴ used free formic or acetic acid with the intention of suppressing the formation of secondary and tertiary amines. The use of acetic acid with ammonium formate at 155° is reported to result in the formation of the acetate salt of the primary amine rather than the formyl derivative; acetophenone and ammonium formate give α -formylaminoethylbenzene, while the addition of acetic acid is stated to lead to the formation of α -aminoethylbenzene acetate.⁴²

The ketone and ammonium formate or formamide are usually employed in a molecular ratio of 1:4 or 1:5. The excess of ammonium formate tends to diminish the formation of secondary or tertiary amines, but ratios higher than 1:4 or 1:5 appear to be of little advantage. In a

series of experiments with acetophenone the percentage yields of amine were 53, 62, 72, and 73, respectively, when the molar ratios of reagent to ketone were 1:3, 1:3.5, 1:4, and 1:5.⁶ Benzophenone and formamide in the ratio of 1:6 give 43% yields of *N*-benzohydrilformamide. Under the same conditions benzophenone and ammonium formate gave a 92% yield. The addition of ammonium formate or magnesium chloride to the benzophenone-formamide reaction mixture increased the yield of *N*-benzohydril formamide to 95%; the addition of ammonium sulfate was not so effective. With benzophenone and formamide in the absence of a catalyst the ratio of 1:18 was necessary in order to obtain a yield of 87%.^{12a}

Temperature

The Leuckart reaction should be carried out at the lowest temperature that will produce the desired product. With dry ammonium formate, it has been necessary to heat the reagents in a sealed tube at 210–240° for several hours. However, the use of an excess of formic acid or a mixed ammonium formate-formamide reagent has made it possible to carry out the reaction at a much lower temperature.⁶ With such a reagent, the reaction can be accomplished by refluxing at atmospheric pressure, usually at temperatures in the range 150–180°; however, temperatures of 175–190° for several hours are required for the conversion of hindered ketones of the terpenoid series. Most reaction periods have been in the range of six to twenty-five hours at 160–185°, but a few reactions with formamide have been carried out by refluxing the reagents for as long as thirty hours.³¹ The heating may be interrupted and resumed as desired.

In a comparative study of the condensation of α -methylphenylacetone with the reagent from ammonia and formic acid, the percentage yields of α,β -dimethyl- β -phenethylamine were 23, 47, and 50, respectively, when the reactions were run for fifteen hours at 190–200°, 170–180°, and 160–170°. Experiments in which the reaction mixture was heated for six hours at 190–200° and seven hours at 160–170° gave yields of 50%. With hindered ketones, such as menthone, camphor, and fenchone, it is advisable to heat at temperatures of 180–230°⁴ or at 175–190°⁶ for a period of twelve to twenty hours in order to obtain maximum yields.

Solvent

Most of the Leuckart reactions are carried out in the absence of any solvent other than the reagents themselves. Mixtures containing a considerable proportion of formamide usually dissolve the ketone or

aldehyde upon heating. However, nitrobenzene has been used as a solvent with a few ketones that were insoluble in the hot reaction mixture, and it has been used to increase the reflux temperature of reaction mixtures containing low-boiling ketones.^{6,10}

Hydrolysis

The formyl derivatives obtained as intermediates in the reaction may be hydrolyzed to the amines by refluxing with acid or alkali. The use of 100–200 ml. of concentrated or 1:1 hydrochloric acid for each mole of ketone appears to be generally satisfactory, and the reaction is usually complete in from thirty minutes to one and one-half hours.^{6,13} When the entire reaction mixture is subjected to hydrolysis it may sometimes be desirable to employ concentrated hydrochloric acid, whereas if the formyl derivative is isolated and purified a 10% solution of hydrochloric acid may give better results.¹² Hydrolysis with 30% aqueous sodium hydroxide usually requires from twelve to twenty hours of refluxing, and the yield of amine is not as good.⁴¹ In the alkaline hydrolysis of the material obtained by interaction of formamide and methyl α -phenyl-*n*-butyl ketone the yield of amine is only 5.3%, but when acid hydrolysis is employed the yield of amine is 86% based on the formyl derivative.²⁵ However, in the production of certain amines, such as thujylamine, it is desirable to hydrolyze the formyl derivative with alkali, inasmuch as acid solutions cause decomposition of the product.²⁵

Isolation

The method of isolation of the free amine directly or following the hydrolysis of the formyl derivative varies with the properties of the product and the procedure used in hydrolysis. After an alkaline hydrolysis, the reaction mixture is extracted with an inert solvent, such as ether or benzene, and the amine is isolated by distillation or by conversion to the hydrochloride. Following an acid hydrolysis, the reaction mixture is cooled and neutralized with alkali before extraction with the inert solvent. Amines of higher molecular weight sometimes separate as crystalline salts directly from the cooled acid hydrolysis mixture. When a salt of the amine, rather than the formyl derivative, is present in the reaction mixture it is only necessary to neutralize the cooled mixture with alkali before extraction with the inert solvent.

EXPERIMENTAL PROCEDURES

Tri-*n*-amylamine ⁴⁴

(Use of Ammonium Formate and Formic Acid)

A mixture of 20 g. of valeraldehyde, 30 g. of ammonium formate, and 10 ml. of formic acid is heated in a round-bottomed flask, equipped with a reflux condenser and suspended in a paraffin bath. The reaction begins at 90°, but the temperature is raised slowly to 130° and maintained there for three hours. The cooled residue is extracted with ether to remove the small quantity of non-basic material, and the base is liberated from the formate salt in the aqueous solution by neutralization with alkali. The base is separated, dried over solid potassium hydroxide, and distilled over sodium in a stream of hydrogen; it boils at 265–270°.

N,N-Dimethylfurfurylamine ^{27,26}

(Use of Dimethylformamide and Formic Acid)

A mixture of 173 g. (2.5 moles) of dimethylformamide (b.p. 145–160°) and 54 g. (1 mole) of 85% formic acid is poured into a 1-l. distilling flask connected to a condenser. A dropping funnel is fitted into the neck of the flask so that its stem extends below the surface of the liquid. The flask is placed in an oil bath, the temperature of which is raised to 150–155°. Over a period of four to five hours, a mixture of 96 g. (1 mole) of redistilled furfural and 163 g. (3 moles) of 85% formic acid is added from the dropping funnel. The water and formic acid which distil are discarded. When all the furfural solution has been added, the receiver is changed and the temperature of the bath is gradually raised as long as distillation occurs. The distillate is made strongly acidic with dilute sulfuric acid, and the furfural and furfuryl alcohol are removed by steam distillation. The acid mixture is then made strongly alkaline by the cautious addition of sodium hydroxide solution; large amounts of dimethylamine are evolved. The alkaline mixture is steam-distilled to remove the tertiary amines. The N,N-dimethylfurfurylamine, which separates from the distillate upon the addition of 40% sodium hydroxide solution, is removed and the aqueous layer extracted twice with benzene. The base and benzene extracts are combined and dried over solid potassium hydroxide for twelve hours. The solvent is removed, and the residue is fractionated; the N,N-dimethylfurfuryl-

⁴⁴ Nabenhauer, private communication.

amine boils at 139–145°. Redistillation of the lower-boiling fractions yields more of the product. The pure base is obtained upon redistillation; b.p. 145–146°; yield 75 g. (60%).

α -(β -Naphthyl)ethylamine ⁶⁴²

(Preparation and Use of Formamide-Formic Acid Reagent from Ammonium Carbonate-Carbamate and Formic Acid)

A 1-l. flask, containing 215 g. (4 mole equivalents of ammonia) of commercial ammonium carbonate-carbamate, is fitted with a cork bearing a thermometer that extends nearly to the bottom of the flask, a small separatory funnel, and a wide, bent tube attached to a short, wide condenser set for distillation. There is then added cautiously 215–230 g. (4.1 moles) of commercial 85–90% formic acid. When the reaction moderates, the mixture is heated cautiously and then slowly distilled until the temperature is about 165°. (The same amount of reagent can be prepared by distillation of 250 g. of commercial solid ammonium formate.) To the hot mixture 173 g. (1 mole) of β -acetone naphthone is added, the bent tube is replaced by a 20- to 30-cm. distilling column, and the heating is continued with a small flame. Water, ammonia, carbon dioxide, and a small amount of ketone distil. Some of the solid ketone and ammonium carbonate collect in the upper part of the column. This material may be removed with the aid of a little concentrated formic acid and returned to the reaction mixture. The mixture gradually becomes homogeneous as the reaction proceeds.

The distillation of water practically ceases when the temperature reaches 175–185°; the temperature of the mixture is then maintained at 175–185° for three to five hours. Termination of the reaction is indicated when the deposition of ammonium carbonate in the condenser no longer occurs. The mixture is cooled and stirred thoroughly with twice its volume of water. The aqueous layer is separated; formamide may be recovered from it. The crude, water-insoluble material is refluxed for forty to fifty minutes with 100 ml. of concentrated hydrochloric acid. The small amount of material that does not dissolve in the acid is extracted with small portions of warm benzene and discarded. The amine hydrochloride crystallizes from the cooled acid solution. It is collected and recrystallized from boiling water; the yield is 174 g. (84%), m.p. 198–199°.

Methyl-*tert*-butylcarbinamine ^{8,10}

(Use of a Solvent, Nitrobenzene)

To a flask containing the Leuckart reagent, prepared as described in the first paragraph of the preceding section, is added 100 g. (1 mole) of pinacolone dissolved in 100-150 g. of nitrobenzene. The reaction is carried out as described above, except that a heating period of about eight hours is required and it is difficult to maintain the temperature at a level higher than about 150-160°. The nitrobenzene and ketone which distil are returned to the reaction mixture from time to time. The nitrobenzene and unchanged pinacolone are removed by steam distillation following the hydrolysis of the formyl derivatives. The acid solution is then neutralized with sodium hydroxide, and the amine is distilled with steam into an excess of hydrochloric acid solution. The acidic solution is evaporated almost to dryness, treated cautiously with saturated potassium hydroxide solution, and extracted with ether. The ether solution of the amine is dried with sodium hydroxide flakes and distilled. The product boils at 102-103°; the yield is 52 g. (52%).

***o*-*p*-Chlorophenethylamine** ¹⁰

(Use of Formamide and Formic Acid)

A 1-l. round-bottomed flask, to which a narrow side tube has been attached for the insertion of a thermometer, is connected by a 19/38 or larger glass joint to an upright water-cooled condenser. The top of this condenser is joined by a wide, bent tube to a short condenser, arranged for downward distillation, and also is fitted with a small separatory funnel. The flask is charged with 310 g. (2 moles) of *p*-chloroacetophenone, 370 g. (about 8 moles) of 90-97% formamide, and 25 ml. of 90% formic acid. The flask is heated with a small flame; the mixture becomes homogeneous, and mild ebullition begins at about 160-165°. The temperature then rises somewhat, refluxing occurs, and a deposit of ammonium carbonate soon appears in the condenser. To prevent clogging and to maintain a slightly acidic reaction mixture, 20- to 25-ml. portions of 90% formic acid are added through the separatory funnel whenever ammonium carbonate is deposited or the odor of ammonia is detected.

The optimum reaction temperature is 175-180°; whenever it falls below about 165-170°, accumulated water is allowed to distil (by draining the reflux condenser) until the temperature rises again. Any ketone that distils with the water should be separated and returned. It is

necessary to add a total of 200–250 ml. (4.5–5.0 moles) of formic acid, and the reaction requires ten to fourteen hours, depending upon the average temperature that has been maintained. The process may be interrupted and resumed at any time. The reaction is considered complete when ammonium carbonate is deposited only very slowly in the condenser.

When the reaction is complete the mixture is cooled and extracted with 250–300 ml. of benzene in several portions. The insoluble portion, chiefly formamide, is retained for recovery or may be used without purification for the next run. The benzene extract is distilled to remove the benzene, and the residue is refluxed for about an hour with 200 ml. of concentrated hydrochloric acid (sp. gr. 1.18). The cold mixture is extracted with benzene in order to remove a small amount (10–12 g.) of oily, acid-insoluble material; the benzene extract is discarded.

The aqueous portion is made strongly alkaline with 20–30% sodium hydroxide solution and distilled with steam until practically no more water-insoluble distillate is obtained; about 2.5–3 l. of distillate usually is sufficient. About 18–20 g. of nonvolatile, basic residue, presumably higher amines, remains in the distillation vessel. The distilled amine is extracted with 200–300 ml. of benzene and is dried by distillation of the benzene. The amine is best distilled under reduced pressure; b.p. 103–104°/11 mm.; yield 254–270 g. (82–87%). A small residue of less volatile material remains in the distilling flask.

α -Aminododecylbenzene ¹²

(Use of Ammonia and Formic Acid)

One hundred and five grams (1.72 moles) of 28% aqueous ammonia and 88 g. (1.72 moles) of 90% formic acid are mixed carefully and poured into a 500-ml. three-necked flask, equipped with a dropping funnel, thermometer, and downward-directed condenser. The temperature is raised to 160° by distilling out water, and 89.5 g. (0.344 mole) of laurophenone is added in one portion. The temperature is maintained at 160–170° for twenty-two hours, and any ketone which distills is returned to the flask at intervals. The formyl derivative is hydrolyzed in the reaction mixture by refluxing for eight hours with 120 ml. of concentrated hydrochloric acid. After twelve hours at room temperature, 200 ml. of water is added and the compact crystalline mass of the hydrochloride is broken up with a glass rod and collected on a Büchner funnel. The α -aminododecylbenzene hydrochloride is washed three times with small portions of cold water and recrystallized from boiling water. The product weighs 76 g. (78%) and after recrystallization from boiling anhydrous ethanol melts at 115–116°.

*α -(*o*-Chlorobenzyl)ethylamine*²¹

(Use of Formamide)

A mixture of 21 g. of *o*-chlorobenzyl methyl ketone and 50 g. of formamide in a 500-ml. flask is refluxed for thirty hours. The mixture is cooled, 100 ml. of 30% sodium hydroxide solution is added, and the alkaline mixture is refluxed for twelve hours to hydrolyze the formyl derivative of the amine. After cooling to room temperature, the reaction mixture is extracted with several portions of ether and the combined ether extract is shaken with 10% hydrochloric acid. Unchanged ketone may be recovered from the ether layer. The amine is recovered from the acid layer by the addition of sodium hydroxide and extraction with ether. The ether solution of the amine is dried over potassium hydroxide sticks and filtered. Dry hydrogen chloride gas is passed into the ether solution, and the precipitated hydrochloride of α -*o*-chlorobenzylethylamine is filtered and dried in a vacuum desiccator. The yield of amine hydrochloride is 15 g. (52%); m.p. 175-176°.

N,N-Dimethylbenzylamine⁹

(Eschweiler-Clarke Procedure)

One hundred and seven grams (1 mole) of benzylamine is added, with cooling, to 235 g. (5 moles) of 90% formic acid. Then 188 g. (2.2 moles) of 35% formaldehyde solution is added, and the mixture is heated on the steam bath under reflux for two to four hours after evolution of gas has ceased (eight to twelve hours in all). About 85 ml. (slightly more than one mole) of concentrated hydrochloric acid is then added, and the formic acid and any excess formaldehyde are evaporated on a steam bath. The colorless residue is dissolved in water and made alkaline by the addition of 25% aqueous sodium hydroxide, and the mixture is steam-distilled. The distillate is saturated with potassium hydroxide; the oil is separated, dried by heating with solid potassium hydroxide, and distilled over sodium. About 108 g. (80%) of *N,N*-dimethylbenzylamine, b.p. 176-180°, is obtained.

TABULAR SURVEY OF THE LEUCKART REACTION

In the tables which follow, examples of the Leuckart reaction described in the literature through 1945 have been tabulated. It is probable that the list is incomplete because the reaction frequently has been used as one step in a synthesis without being indexed or referred to as a Leuckart

process. Since many of these reactions were carried out before the development of the modified procedures, it is likely that yields reported do not always represent the best that could be obtained. The arrangement of the carbonyl compounds in each table, or in groups of closely related compounds within a table, is alphabetical, and for each carbonyl compound the amines which react with it are also listed in alphabetical order.

TABLE I

LEUCKART REACTIONS WITH ALIPHATIC ALDEHYDES

| Aldehyde | Reagent | Product | Yield % | Reference |
|---------------|--|--|---------------------|-----------|
| Butyraldehyde | Piperazine + formic acid | N,N'-Dibutylpiperazine | 61 | 22 |
| Formaldehyde | Ammonia + formic acid | Trimethylamine | — | 7 |
| Formaldehyde | Benzylamine + formic acid | N,N-Dimethylbenzylamine | 80 | 8, 9, 15 |
| Formaldehyde | Butylamine + formic acid | N,N-Dimethylbutylamine | 80 | 9 |
| Formaldehyde | β -(2,5-Dimethoxyphenyl)ethylamine + formic acid | N,N-Dimethyl- β -(2,5-dimethoxyphenyl)ethylamine | Almost quantitative | 17 |
| Formaldehyde | β -(2,5-Dimethoxyphenyl)isopropylamine + formic acid | N,N-Dimethyl- β -(2,5-dimethoxyphenyl)isopropylamine | Almost quantitative | 17 |
| Formaldehyde | β -(2,5-Dimethoxyphenyl)propylamine + formic acid | N,N-Dimethyl- β -(2,5-dimethoxyphenyl)propylamine | Almost quantitative | 17 |
| Formaldehyde | Ethylamine + formic acid | N,N-Dimethylethylamine | — | 8 |
| Formaldehyde | Ethylenediamine + formic acid | Tetramethyl-1,2-diaminoethane | — | 8 |
| Formaldehyde | Tetramethyl-1,4-diaminobutane + formic acid | Tetramethyl-1,4-diaminobutane | 90 | 8 |
| Formaldehyde | Aniline + formic acid | N-Methylaniline | — | 15 |
| Formaldehyde | Benzylamine + formic acid | N-Methylbenzylamine | Almost quantitative | 17 |
| Formaldehyde | Benzylbutylamine + formic acid | Methylbenzylbutylamine | Almost quantitative | 17 |
| Formaldehyde | Benzyldecylamine + formic acid | Methylbenzyldecylamine | Almost quantitative | 17 |
| Formaldehyde | Benzylethylamine + formic acid | Methylbenzylethylamine | Almost quantitative | 17 |
| Formaldehyde | Benzylmethylamine + formic acid | Methylbenzylmethylamine | Almost quantitative | 17 |
| Formaldehyde | Benzylpropylamine + formic acid | Methylbenzylpropylamine | Almost quantitative | 17 |
| Formaldehyde | Dibenzylamine + formic acid | Methyldibenzylamine | 73 | 8 |
| Formaldehyde | β -(2,5-Dimethoxyphenyl)ethylmethylamine + formic acid | N,N-Dimethyl- β -(2,5-dimethoxyphenyl)ethylamine | Almost quantitative | 17 |
| Formaldehyde | β -(4-Methoxyphenyl)ethylbenzylamine + formic acid | N-Methyl- β -(4-methoxyphenyl)ethylbenzylamine | Almost quantitative | 17 |
| Formaldehyde | Piperazine + formic acid | N,N'-Dimethylpiperazine | — | 8 |
| Formaldehyde | Piperidine + formic acid | N-Methylpiperidine | 80 | 8 |
| Formaldehyde | Mexidine + formic acid | N,N-Dimethylmexidine | 73 | 21 |
| Formaldehyde | p-Toluidine + formic acid | N,N-Dimethyl-p-toluidine | — | 20 |
| Formaldehyde | 2,4,6-Tribromoaniline + formic acid | N,N-Dimethyl-2,4,6-tribromoaniline | 77 | 8 |
| Formaldehyde | α -Aminoisobutyric acid + formic acid | α -Dimethylaminoisobutyric acid | 80 | 8 |
| Formaldehyde | β -Aminopropionic acid + formic acid | β -Dimethylaminopropionic acid | 38 | 8 |
| Formaldehyde | Glycine + formic acid | N,N-Dimethylglycine | 60-70 | 8 |
| Formaldehyde | α -Phenyl- α -aminobutyric acid + formic acid | α -Phenyl- α -dimethylaminobutyric acid | 72 | 9 |
| Valeraldehyde | Ammonium formate + formic acid | Trimethylamine | — | 49 |
| Valeraldehyde | Aniline + formic acid | N,N-Dimethylaniline | — | 49 |
| Valeraldehyde | Methylamine + formic acid | N-Amethyl-N-methylaniline | — | 49 |

TABLE II

LEUCKART REACTIONS WITH AROMATIC AND HETEROCYCLIC ALDEHYDES

| Aldehyde | Reagent | Product | Yield % | Reference |
|------------------------|--|--|-------------------------|------------|
| <i>o</i> -Anisaldehyde | Ethylamine + formic acid | N-Ethyl- <i>o</i> -anisylamine | — | 23 |
| <i>o</i> -Anisaldehyde | Methylamine + formic acid | N-Methyl- <i>o</i> -anisylamine | — | 23 |
| <i>m</i> -Anisaldehyde | Ethylamine + formic acid | N-Ethyl- <i>m</i> -anisylamine | — | 23 |
| <i>p</i> -Anisaldehyde | Ethylamine + formic acid | N-Ethyl- <i>p</i> -anisylamine | — | 23 |
| <i>p</i> -Anisaldehyde | Methylamine + formic acid | N-Methyl- <i>p</i> -anisylamine | — | 23 |
| Benzaldehyde | Ammonium formate | Tribenzylamine, dibenzylamine, benzylamine | 25-40 10-15 Trace | 1 |
| Benzaldehyde | Ammonium formate + formic acid | Tribenzylamine | — | 4; |
| Benzaldehyde | Aniline + formic acid | N-Benzylamine | — | 4; |
| Benzaldehyde | Ethanolamine + formamide | N-Hydroxyethylbenzylamine | — | 57 |
| Benzaldehyde | Ethylamine + formic acid | N-Ethylbenzylamine | — | 4; |
| Benzaldehyde | 3-Methyl-2-phenylpropanamine + formic acid | N-Benzyl-3-methyl-2-phenylpropanamine | — | 4; |
| Benzaldehyde | Piperazine + formic acid | N,N'-Dibenzylpiperazine | 84 | 22 |
| Benzaldehyde | Piperidine + formic acid | N-Benzylpiperidine | — | 4; |
| Benzaldehyde | Piperidine + methyl formate | N-Benzylpiperidine | — | 26 |
| Furfural | Diethylamine + formic acid | N,N-Diethylfurfurylamine | — | 27 |
| Furfural | Dimethylamine + formic acid | N,N-Dimethylfurfurylamine | 65 | 26, 27, 28 |
| Furfural | Formamide | Furfurylamine | — | 28 |
| Furfural | Methylamine + formic acid | N-Methylfurfurylamine | — | 28 |
| Furfural | Methylformamide + formic acid | N-Methyl- <i>N</i> -methylfurfurylamine | — | 28 |
| Furfural | Morpholine + formic acid | N-Furfurylmorpholine | — | 28 |

* Wegler, U. S. pat. 2,251,245 [C.A., 35, 6975 (1941)].

TABLE III
LEUCKART REACTIONS WITH ALIPHATIC KETONES

| Ketone | Reagent | Product | Yield % | Reference |
|--|--|---|---------|------------|
| Acetone | α -Naphthylamine + methyl formate | N-Isopropyl- α -naphthylamine | — | 23 |
| Diethyl ketone | Ammonium formate + acetic acid | 3-Pentylamine | — | 49 |
| Di-n-heptyl ketone | Ammonia + formic acid | 8-Nona-decylamine | 40 | 12 |
| Diisobutyl ketone | Formamide + formic acid | 3,6-Dimethyl-14-heptylamine | 77 | 10 |
| Diisopropyl ketone | Formamide + formic acid | 2,4-Dimethyl-13-pentylamine | 64 | 10 |
| Di-n-propyl ketone | Formamide + formic acid | 4-Heptylamine | 23 | 10 |
| Methyl amyl ketone | Ammonium carbonate-carbamate + formic acid | 3-Heptylamine | 23 | 10 |
| Methyl amyl ketone | Ammonium formate | 2-Heptylamine | 53 | 29 |
| Methyl butyl ketone | Ammonium formate | 2-Hexylamine | — | 29 |
| Methyl cyclohexyl ketone | Ammonium formate | α -Cyclohexylethylamine | — | 30 |
| Methyl hexyl ketone | Ammonium formate | 2-Octylamine | — | 5, 23 |
| Methyl hexyl ketone | Formamide + formic acid | 3-Octylamine | 60 | 10 |
| Methyl propyl ketone | Ammonium carbonate-carbamate + formic acid | 3-Pentylamine | 10-37 | 10 |
| Methyl octadecyl ketone | Ethanolamine + methyl formate | N-Ethoxyethyl-3-octylamine | 85 | 37 |
| Pinacolone | Ammonium carbonate-carbamate + formic acid | 3,5-Dimethyl-13-butylamine | 62 | 6 |
| α -Chlorophenylacetone | Formamide | β - α -Chlorophenylisopropylamine | 52 | 31 |
| Di-(bromoveratryl) ketone | Ammonium carbonate + formic acid | Di-(bromoveratryl)isopropylamine | — | 37 |
| α,α -Dimethylphenylacetone | Formamide | β,β -Dimethyl- α -phenylisopropylamine | 75 | 35 |
| Diphenylacetone | Ammonium formate | Dibenzylcarbamate | — | 39 |
| Diveratryl ketone | Ammonium carbonate + formic acid | Diveratrylcarbamate | — | 34 |
| α -Ethylphenylacetone | Formamide | β -Ethyl- α -phenylisopropylamine | 63 | 35 |
| p-Fluorophenylacetone | Formamide | β -p-Fluorophenylisopropylamine | — | 35 |
| 3,4-Methylenedioxyphenylacetone | Ammonia + formic acid | β -3,4-Methylenedioxyphenylisopropylamine | 20 | 34 |
| α -Methylphenylacetone | Ammonia + formic acid | β -Methyl- α -phenylisopropylamine | 53 | 12 |
| α -Methylphenylacetone | Butylamine + formic acid | N-Ethyl- α -methyl- α -phenylisopropylamine | 74 | 12 |
| α -Methylphenylacetone | Formamide | β -Methyl- α -phenylisopropylamine | 60 | 35 |
| α -Methylphenylacetone | Methylamine + formic acid | N- β -Dimethyl- α -phenylisopropylamine | 15, 41 | 12, 35 |
| Phenylacetone | Ammonia + formic acid | β -Phenylisopropylamine | 27 | 12, 32 |
| Phenylacetone | Ammonium formate | β -Phenylisopropylamine | — | 33 |
| Phenylacetone | Amylamine + formic acid | N-Amyl- β -phenylisopropylamine | 50-70 | 32 |
| Phenylacetone | Butylamine + formic acid | N-Butyl- β -phenylisopropylamine | 50-70 | 12, 32 |
| Phenylacetone | Diethylamine + formic acid | N,N-Diethyl- β -phenylisopropylamine | 50-70 | 32 |
| Phenylacetone | Dimethylamine + formic acid | N,N-Dimethyl- β -phenylisopropylamine | 50-70 | 32 |
| Phenylacetone | Ethylamine + formic acid | N-Ethyl- β -phenylisopropylamine | 50-70 | 32 |
| Phenylacetone | Formamide | β -Phenylisopropylamine | 50-60 | 31 |
| Phenylacetone | Methylamine + formic acid | N-Methyl- β -phenylisopropylamine (22) | 50-70 | 12, 22, 35 |
| α -Propylphenylacetone | Formamide | β -Propyl- α -phenylisopropylamine | 63 | 35 |
| α -Tolylacetone | Formamide | β - α -Tolylisopropylamine | — | 33 |
| α -Tolylacetone | Methylamine + formic acid | N-Methyl- β - α -tolylisopropylamine | — | 33 |
| m -Tolylacetone | Formamide | β - m -Tolylisopropylamine | — | 33 |
| m -Tolylacetone | Methylamine + formic acid | N-Methyl- β - m -tolylisopropylamine | — | 33 |
| p-Tolylacetone | Formamide | β -p-Tolylisopropylamine | — | 33 |
| p-Tolylacetone | Methylamine + formic acid | N-Methyl- β -p-tolylisopropylamine | — | 33 |

TABLE IV

LEUCKART REACTIONS WITH ALIPHATIC-AROMATIC AND ALIPHATIC-HETEROCYCLIC KETONES

| Ketone | Reagent | Product | Yield % | Reference |
|-----------------------------|--|--|---------|-----------|
| Acetophenone | Ammonium formate | α -Phenethylamine | — | 47, 40 |
| Acetophenone | Ammonium formate + acetic acid | α -Phenethylamine | — | 47 |
| Acetophenone | Ammonium carbonate-carbamate + formic acid | α -Phenethylamine | 72-81 | 6, 10, 43 |
| Acetophenone | Aniline + methyl formate | N- α -Phenethylamine | — | 23 |
| Acetophenone | Butylamine + formic acid | N-Butyl- α -phenethylamine | 78 | 13 |
| Acetophenone | Ethylamine + formic acid | N-Ethyl- α -phenethylamine | 70 | 13 |
| Acetophenone | Formamide | α -Phenethylamine | 50-60 | 31, 41 |
| Acetophenone | Hydroxyethylformamide | N-Hydroxyethyl- α -phenethylamine | 60 | 57 |
| Acetophenone | Methylamine + formic acid | N-Methyl- α -phenethylamine | 60 | 13 |
| Acetophenone | α -Naphthylamine + methyl formate | N- α -Phenylethyl- α -naphthylamine | — | 23 |
| Acetophenone | 1,3-Propanolamine + formamide | N- γ -Hydroxypropyl- α -phenethylamine | 42 | 57 |
| p-Bromoacetophenone | Ammonium carbonate-carbamate + formic acid | α -p-Bromophenethylamine | 79 | 6 |
| p-Bromoacetophenone | Ammonium formate | α -p-Bromophenethylamine | 63 | 40 |
| p-Bromoacetophenone | Butylamine + formic acid | N-Butyl- α -p-bromophenethylamine | 70 | 13 |
| p-Bromoacetophenone | Ethylamine + formic acid | N-Ethyl- α -p-bromophenethylamine | 60 | 13 |
| p-Bromoacetophenone | Methylamine + formic acid | N-Methyl- α -p-bromophenethylamine | 70 | 13 |
| p-Bromoheptanophenone | Ammonia + formic acid | α -p-Bromophenylheptylamine | — | 23 |
| p-Bromohexanophenone | Ammonia + formic acid | α -p-Bromophenylhexylamine | — | 12 |
| p-Chloroacetophenone | Ammonia + formic acid | α -p-Chlorophenethylamine | 82 | 6 |
| p-Chloroacetophenone | Ammonium formate | α -p-Chlorophenethylamine | 65 | 40 |
| p-Chloroacetophenone | Butylamine + formic acid | N-Butyl- α -p-chlorophenethylamine | 60 | 13 |
| p-Chloroacetophenone | Ethylamine + formic acid | N-Ethyl- α -p-chlorophenethylamine | 60 | 13 |
| p-Chloroacetophenone | Methylamine + formic acid | N-Methyl- α -p-chlorophenethylamine | 70 | 13 |
| p-Chloroheptanophenone | Ammonia + formic acid | α -p-Chlorophenylheptylamine | — | 12 |
| p-Chlorohexanophenone | Ammonia + formic acid | α -p-Chlorophenylhexylamine | — | 12 |
| p-Dimethylaminolaurophenone | Ammonia + formic acid | α -p-Dimethylaminophenyldodecylamine | — | 7 |
| p-Dodecylacetophenone | Ammonium formate | α -p-Dodecylphenethylamine | — | 42, 43 |
| Isobutyrophenone | Formamide + formic acid | α -Phenylisobutylamine | 85 | 10 |
| Laurophenone | Ammonia + formic acid | α -Phenyldodecylamine | 78 | 12, 43 |
| Laurophenone | Dimethylamine + formic acid | No product when heated at 160-170° for twenty-eight hours. | — | 12 |
| Laurophenone | Methylamine + formic acid | N-Methyl- α -phenyldodecylamine | 53 | 12 |
| p-Methoxyacetophenone | Ammonium carbonate-carbamate + formic acid | α -p-Methoxyphenethylamine | 63 | 6 |
| p-Methoxylaurophenone | Ammonia + formic acid | α -p-Methoxyphenyldodecylamine | — | 7 |

TABLE IV—Continued

LEUCKART REACTIONS WITH ALIPHATIC-AROMATIC AND ALIPHATIC-HETEROCYCLIC KETONES

| Ketone | Reagent | Product | Yield % | Reference |
|------------------------------|--|--|----------------|-----------|
| <i>o</i> -Methylacetophenone | Ammonium carbonate-carbamate + formic acid | <i>o</i> -Tolylethylamine | 70 | 8 |
| <i>p</i> -Methylacetophenone | Ammonium carbonate-carbamate + formic acid | <i>o</i> - <i>p</i> -Tolylethylamine | 72 | 8 |
| <i>p</i> -Methylacetophenone | Ammonium formate | <i>o</i> - <i>p</i> -Tolylethylamine | 72 | 40 |
| <i>p</i> -Methylacetophenone | Butylamine + formic acid | <i>N</i> -Butyl- <i>o</i> - <i>p</i> -tolylethylamine | 50 | 13 |
| <i>p</i> -Methylacetophenone | Ethylamine + formic acid | <i>N</i> -Ethyl- <i>o</i> - <i>p</i> -tolylethylamine | 80 | 13 |
| <i>p</i> -Methylacetophenone | Formamide | <i>o</i> - <i>p</i> -Tolylethylamine | 50-80 | 31 |
| <i>p</i> -Methylacetophenone | Methylamine + formic acid | <i>N</i> -Methyl- <i>o</i> - <i>p</i> -tolylethylamine | 80 | 13 |
| <i>p</i> -Methylacetophenone | Ammonia + formic acid | <i>o</i> - <i>p</i> -Tolylethylamine | 63 | 13 |
| <i>p</i> -Methylacetophenone | Ammonia + formic acid | <i>o</i> - <i>p</i> -Tolyldecylamine | — | 7 |
| <i>m</i> -Nitroacetophenone | Ammonium carbonate-carbamate + formic acid | <i>m</i> -Nitrophenethylamine | 58 | 8 |
| <i>p</i> -Thioxyacetophenone | Ammonium carbonate-carbamate + formic acid | <i>o</i> - <i>p</i> -Thioxyphenethylamine | 69 | 8, 43 |
| <i>p</i> -Thiylacetophenone | Ammonium carbonate-carbamate + formic acid | <i>o</i> - <i>p</i> -Xenylethylamine | 77 | 8 |
| <i>p</i> -Thiylacetophenone | Ammonium formate | <i>o</i> - <i>p</i> -Xenylethylamine | 66 | 40 |
| Propiophenone | Ammonia + formic acid | <i>o</i> -Thiylpropylamine | 68 | 10, 13 |
| <i>β</i> -Ictonaphthone | Ammonium carbonate-carbamate + formic acid | <i>o</i> -(3'-Naphthyl)ethylamine | 64 | 8 |
| <i>β</i> -Ictonaphthone | Ammonium formate | <i>o</i> -(3'-Naphthyl)ethylamine | 64 | 40 |
| <i>o</i> -Acetilthione | Ammonium formate | <i>o</i> -(4'-Thienyl)ethylamine | 61 | 43 |
| <i>o</i> -Acetilthione | Methylamine + formic acid | <i>N</i> -Methyl- <i>o</i> -(4'-thienyl)ethylamine | 65 | 43 |
| <i>o</i> -Propiothione | Formamide | <i>o</i> -(4'-Thienyl)propylamine | 36 | 43 |
| <i>o</i> -Propiothione | Methylamine + formic acid | <i>N</i> -Methyl- <i>o</i> -(4'-thienyl)propylamine | 27 | 43 |
| Benzoin | Ammonium carbonate + formic acid and acetic acid | Desylamine | Small quantity | 45 |

TABLE V

LEUCKART REACTIONS WITH AROMATIC KETONES

| Ketone | Reagent | Product | Yield % | Reference |
|---------------------|-----------------------|---------------------------|---------|-----------|
| 1,3-Benzofluorenone | Formamide | 9-Amino-1,3-benzofluorene | — | 49 |
| 2,3-Benzofluorenone | Formamide | 9-Amino-2,3-benzofluorene | — | 49 |
| Benzophenone | Ammonia + formic acid | Benzohydrylamine | 80 | 12, 43 |
| Benzophenone | Ammonium formate | Benzohydrylamine | — | 1 |
| Fluorenone | Formamide | 9-Aminofluorene | 70-75 | 49 |

TABLE VI
LEUCKART REACTIONS WITH ALICYCLIC KETONES

| Ketone | Reagent | Product | Yield % | Reference |
|-----------------------|--|--|----------|-----------|
| Camphor | Ammonium carbonate-carbamate + formic acid | Bornylamines | 62 | 6 |
| Camphor | Ammonium carbonate + formic acid | Bornylamines | 83 | 52 |
| Camphor | Ammonium formate | Bornylamines | 50-60 | 1, 4 |
| Camphor | Methylformamide + formic acid | N-Methylbornylamines | 60-75 | 51 |
| Carvomenthone | Ammonium formate | Carvomenthylamine, } di-carvomenthylamine } | 25 | 53 |
| Cyclohexanone | Ammonium formate + acetic acid | Dicyclohexylamine | — | 47 |
| Cyclohexanone | Benzylamine + formic acid | N-Cyclohexylbenzylamine | — | 47 |
| Cyclohexanone | Cyclohexylamine + methyl formate | Dicyclohexylamine | — | 28 |
| Cyclohexanone | Ethanamine + formamide | N-Hydroxyethylcyclohexylamine | 65 | 57 |
| Cyclohexanone | Formamide + formic acid | Cyclohexylamine, } dicyclohexylamine } | 25 22 | 10, 50 |
| Cyclohexanone | Isopropylamine + methyl formate | N-Cyclohexylisopropylamine | — | 23 |
| Cyclohexanone | α -Naphthylamine + methyl formate | N-Cyclohexyl- α -naphthylamine | — | 23 |
| Cyclohexanone | Piperidine + methyl formate | N-Cyclohexylpiperidine | — | 28 |
| Fenchone | Ammonium carbonate-carbamate + formic acid | Fenchylamine | 85 | 6 |
| Fenchone | Ammonium formate | Fenchylamine | 90 | 4 |
| Menthone | Ammonium formate | Menthylamines | — | 4, 53 |
| 1-Menthone | Ammonium formate + formamide + formic acid | Menthylamines | 80 | 10 |
| 2-Methylcyclohexanone | Formamide + formic acid | 2-Methylcyclohexylamine, } di-2-methylcyclohexylamine } | 60 20 | 10 |
| 2-Methylcyclohexanone | Ammonium formate + formic acid | Di-2-methylcyclohexylamine | — | 47 |
| 2-Methylcyclohexanone | Amylamine + formic acid | N-Amyl-2-methylcyclohexylamine | — | 47 |
| 2-Methylcyclohexanone | Benzylamine + formic acid | N-Benzyl-2-methylcyclohexylamine | — | 47 |
| 2-Methylcyclohexanone | 3-Methylcyclohexylamine + formic acid | Di-3-methylcyclohexylamine | — | 47 |
| Thiujone | Ammonium carbonate-carbamate + formic acid | Thiujylamine | 55-77 | 10, 55 |

TABLE VII
LEUCKART REACTION WITH QUINONE

| Quinone | Reagent | Product | Yield % | Reference |
|---------------|-----------|--|---------|-----------|
| Anthraquinone | Formamide | 9,10-Diamino-9,10-dihydroanthraquinone | 90 | 42 |

CHAPTER 8

SELENIUM DIOXIDE OXIDATION

NORMAN RADJOHN
University of Missouri

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INTRODUCTION

Although it has been known¹ for a long time that organic compounds can be oxidized by selenium dioxide or selenious acid, only in recent years have these oxidizing agents found extensive application. It had been observed frequently that when commercial fuming sulfuric acid was used as an oxidizing agent (for example, in the introduction of hydroxyl groups into anthraquinone and its derivatives) the trace of selenium dioxide present in the acid was the active oxidizing agent.² The first practical use of selenium dioxide is recorded in a patent granted to the I.G. Farbenindustrie in 1930, which disclosed that 2-methylbenzanthrone could be oxidized to benzanthrone-2-carboxaldehyde.³

¹ Gmelin's *Handbuch der anorganischen Chemie*, Verlag Chemie, Berlin, 1907, pp. 756, 764.

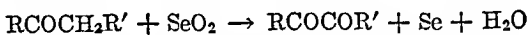
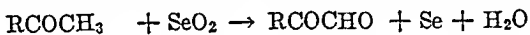
² Brady, *Science Progress*, 28, 100 (1933).

³ I.G. Farbenind. A.-G., Ger. pat. 557,249 (C.A., 27, 304 (1933)).

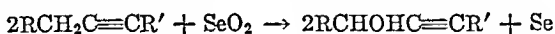
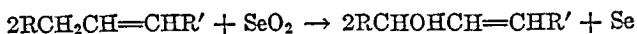
Soon afterwards (1932), Riley, Morley, and Friend⁴ undertook a systematic study of the oxidizing properties of selenium dioxide and showed that it oxidizes aldehydes and ketones of various types to 1,2-dialdehydes, aldoketones, and 1,2-diketones. This represented a marked advance in the method of preparation of many difficultly obtainable compounds and provided the impetus to many further studies of the oxidizing action of selenium dioxide. The results of these studies are the basis on which this chapter is written.

THE NATURE OF THE REACTION

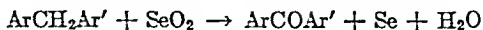
Selenium dioxide oxidation is applicable to synthetic work, structural studies, analytical procedures, and a number of diverse reactions. It is associated generally with the conversion of active methyl or methylene groups to carbonyl groups as illustrated by the following equations.



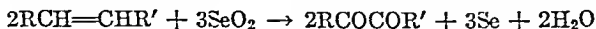
The methyl or methylene groups can be activated by groups other than the carbonyl. Olefins and acetylenes are oxidized at the α -methylenic carbon atom to yield unsaturated alcohols. A methyl or methylene



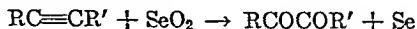
group adjacent to one or more aromatic or heterocyclic rings is also converted to a carbonyl group. In a number of cases, the aldehyde is oxidized further to the corresponding carboxylic acid.



Certain olefins undergo loss of hydrogen and addition of oxygen.



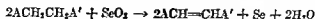
Acetylenic compounds which do not possess an active methylene group also undergo addition of oxygen.



Selenium dioxide can bring about a still different type of reaction whereby oxygen does not enter the final product but the reacting molecule suffers dehydrogenation. Such reactions usually occur in systems where two carbon atoms carrying hydrogen atoms are situated between

⁴ Riley, Morley, and Friend, *J. Chem. Soc.*, 1932, 1875.

activating groups. A and A' may be doubly bonded carbon atoms,

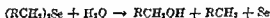
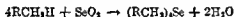


carbonyl groups, ester groups, or aromatic nuclei.

In addition to these more general types of reactions, selenium dioxide will attack paraffin hydrocarbons, alcohols, phenols, mercaptans, sulfides, amines, hydrazines, amides, thioamides, acids, and a large number of other substances.

As yet, no completely satisfactory mechanism has been suggested to explain the varied behavior of selenium dioxide toward the countless organic compounds that it is capable of attacking. Mel'nikov and Rokitskaya⁴⁻¹⁵ have published a series of papers on the mechanism of the selenium dioxide reaction. From a study of the rate constants of the reactions between selenium dioxide and a number of compounds in 75% acetic acid, they concluded that the oxidation takes place through the formation of an intermediate complex. From simple alcohols they were able to isolate dialkyl selenites which could be decomposed thermally to give the corresponding aldehydes, selenium, and water.

Guillemonat¹⁶ has postulated the formation of selenium complexes from a study of the oxidation of 2-methyl-2-butene. He believes that the following series of reactions can occur with an olefin. (R is a radical containing an ethylenic bond.)



⁴ Mel'nikov, *Uspekhi Khim.*, **5**, 443 (1936) [*C.A.*, **30**, 5180 (1936)].

⁵ Mel'nikov, *Fortschr. Chem. (Russ.)*, **5**, 443 (1936) (*Chem. Zentr.*, **1936**, II, 2330).

⁷ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **7**, 1532 (1937) [*C.A.*, **31**, 8502 (1937)].

⁸ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **7**, 2733 (1937) [*C.A.*, **32**, 2903 (1938)].

⁹ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **8**, 834 (1938) [*C.A.*, **33**, 1267 (1939)].

¹⁰ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **8**, 1369 (1938) [*C.A.*, **33**, 4194 (1939)].

¹¹ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **9**, 1158 (1939) [*C.A.*, **34**, 1233 (1940)].

¹² Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **9**, 1608 (1939) [*C.A.*, **34**, 3676 (1940)].

¹³ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **10**, 1439 (1940) [*C.A.*, **35**, 2400 (1941)].

¹⁴ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **10**, 1713 (1940) [*C.A.*, **35**, 3226 (1941)].

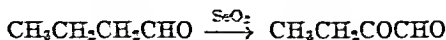
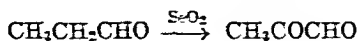
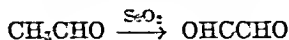
¹⁵ Mel'nikov and Rokitskaya, *J. Gen. Chem. U.S.S.R.*, **15**, 657 (1945) [*C.A.*, **40**, 5702 (1946)].

¹⁶ Guillemonat, *Ann. chim.*, **11**, 143 (1939).

Astin, Moulds, and Riley¹⁷ agree that unstable organoselenium compounds are formed in many selenium dioxide oxidations. However, they maintain that the intermediate-complex theory would require the existence of a large number of different types of unstable compounds; a complicated addition of oxygen then would be necessary in the later stages of the reaction. An investigation¹⁸ of the spectra of substances heated in selenium dioxide vapor suggests that the vapor is capable of providing oxygen atoms in a very low energy state. This may account for the formation of many unstable compounds. The dehydrogenating action of selenium dioxide indicates that the first process in many of the oxidations must be the removal of activated hydrogen atoms. This may or may not be followed by the addition of oxygen in a low energy state according to the nature of the dehydrogenated product.

THE SCOPE OF THE REACTION

The oxidation of compounds containing active methyl or methylene groups is perhaps the most valuable reaction of selenium dioxide. Desirable substances may be obtained from aldehydes and ketones. Even simple aliphatic aldehydes show the characteristic transformation of methylene or methyl groups to carbonyl groups. Acetaldehyde,^{4,11,12} propionaldehyde,^{4,11,12} and *n*-butyraldehyde,^{4,11,12} for example, give yields of 90%, 30%, and 40%, respectively, of glyoxals. In a similar



manner, aliphatic ketones are converted to glyoxals or α -diketones. 2-Butanone^{4,11,12,13} leads to a mixture of ethylglyoxal (17%) and biacetyl (1%), demonstrating the ability of selenium dioxide to attack both active methyl and methylene groups. Cyclic ketones^{4,12} and mixed



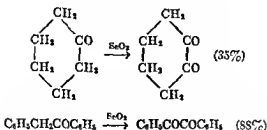
aliphatic-aromatic ketones²⁰ give satisfactory yields of diketones.

¹⁷ Astin, Moulds, and Riley, *J. Chem. Soc.*, 1935, 991.

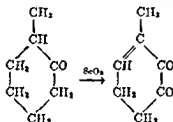
¹⁸ Emmelius and Riley, *Proc. Roy. Soc. London*, 140A, 378 (1933).

¹⁹ Imperial Chem. Ind., Brit. pat. 354,795 (*Chem. Zentr.*, 1922, I, 285).

²⁰ Hatt, Pilgrim, and Hurran, *J. Chem. Soc.*, 1935, 93.



A large number of substituted benzyl ketones has been converted to diketones in very high yields. 2-Methylcyclohexanone²¹ behaves anomalously when treated with selenium dioxide, dehydrogenation as



well as oxidation taking place.

Natural products, such as steroids and terpenes, which contain active methylene groups behave quite normally toward selenium dioxide.



Cholestanone^{22,23} is converted to 2,3-cholestanedione (30%). Camphor^{24,27} and isofenchone^{25,26,28} give the corresponding 1,2-diketones.

²¹ Godchot and Cauquil, *Compt. rend.*, **302**, 326 (1936).

²² Stiller and Rosenheim, *J. Chem. Soc.*, **1933**, 353.

²³ Callow and Rosenheim, *J. Chem. Soc.*, **1933**, 347.

²⁴ Allard, *Bull. ind. pin.*, **1934**, 127 [*C.A.*, **28**, 7235 (1934)].

²⁵ Evans, Ridgion, and Simonsen, *J. Chem. Soc.*, **1934**, 137.

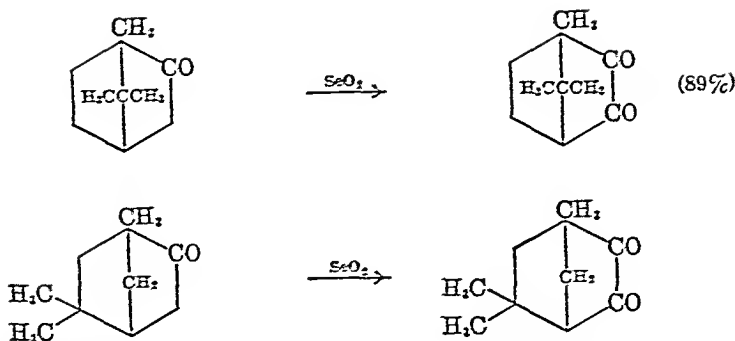
²⁶ Vène, *Compt. rend.*, **216**, 772 (1943).

²⁷ Vène, *Bull. soc. sci. Bretagne*, **19**, 14 (1943-1944) (Pub. 1946) [*C.A.*, **41**, 739 (1947)].

²⁸ Adler, Stein, and Rickert, *Ann.*, **525**, 221 (1936).

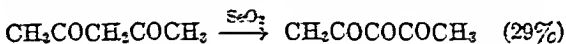
²⁹ Rushentseva and Delektorakaya, *J. Gen. Chem. U.S.S.R.*, **10**, 1653 (1940) [*C.A.*, **33**, 3246 (1941)].

³⁰ Rushentseva and Delektorakaya, *Compt. rend. acad. sci. U.S.S.R.*, **25**, 41 (1940) [*C.A.*, **33**, 3622 (1941)].

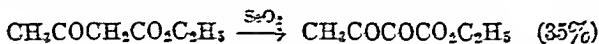


3-Benzylcamphor,^{25,27} on the other hand, suffers dehydrogenation to 3-benzylidenecamphor (95%).

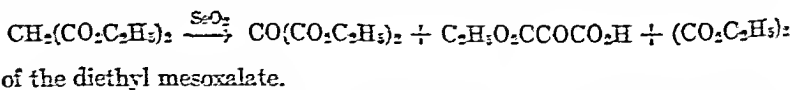
A methylene group situated between two carbonyl groups, a carbonyl and an ester group, two ester groupings, two aromatic nuclei, or an aromatic group and a carboxyl group generally is changed to a carbonyl group. 2,4-Pentanedione²¹ yields 2,3,4-pentanetrione. Ethyl aceto-



acetate²² is transformed to ethyl α,β -diketobutyrate. Diethyl malonate^{13,22,23} gives diethyl mesoxalate (32%), monoethyl mesoxalate, and diethyl oxalate. The last probably results from a disproportionation

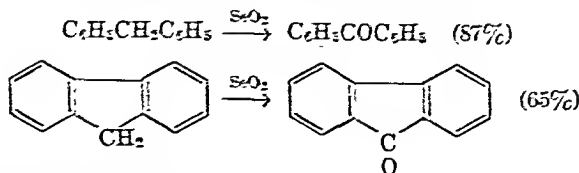


of the diethyl mesoxalate.



of the diethyl mesoxalate.

Diphenylmethane^{24,25,26} and fluorene^{22,27} are oxidized readily to ketones. Indene,²⁸ curiously, is reported to give hydrindene and a hydro-



²¹ Platt, *Gazz. chim. Ital.*, 65, 276 (1935).

²² Müller, *Ber.*, 66, 1668 (1933).

²³ Astin, Newman, and Riley, *J. Chem. Soc.*, 1933, 391.

²⁴ DuPont, Allard, and Dulon, *Bull. soc. chim. France*, [4] 53, 599 (1933).

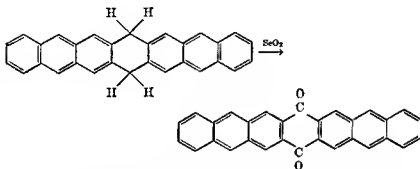
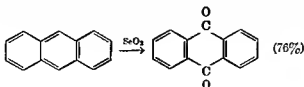
²⁵ Fisher, *J. Am. Chem. Soc.*, 55, 2955 (1933).

²⁶ Postowsky and Lugovskii, *Ber.*, 68, 852 (1935).

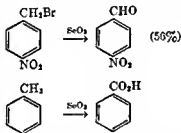
²⁷ Badger, *J. Chem. Soc.*, 1941, 535.

²⁸ Yokoyama, *J. Chem. Soc. Japan*, 59, 252, 271 (1935) [*C.A.*, 32, 9962 (1938)].

carbon C_9H_{10} . Anthracene^{17,38} and 7,16-dihydroheptacene³⁹ are converted to quinones, but phenanthrene^{17,38} is scarcely attacked. Benzyl

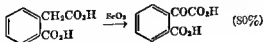


halides^{38,40} yield benzaldehyde (49%), and toluene⁴¹ gives benzoic acid.



Triphenylmethane⁴² is oxidized to triphenylcarbinol (15%).

Homophthalic acid⁴³ and its derivatives^{43,44} demonstrate the activating effect of the benzene ring and the carboxyl group.



³⁸ Clar, *Ber.*, **75**, 1283, 1330 (1942).

³⁹ Michaelis and Landmann, *Ber.*, **13**, 656 (1880).

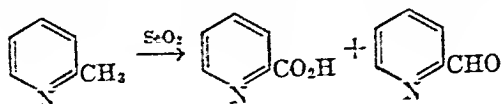
⁴⁰ Deupree and Lyons, *Proc. Indiana Acad. Sci.*, **46**, 101 (1937) [*C.A.*, **32**, 498 (1938)].

⁴¹ Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, **11**, 715 (1934) [*C.A.*, **29**, 1080 (1935)].

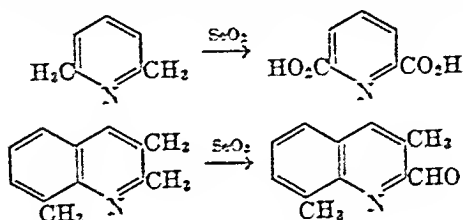
⁴² Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, **11**, 673 (1934) [*C.A.*, **29**, 2942 (1935)].

⁴³ Chakravarti, Swaminathan, and Venkataraman, *J. Indian Chem. Soc.*, **17**, 264 (1940) [*C.A.*, **34**, 6254 (1940)].

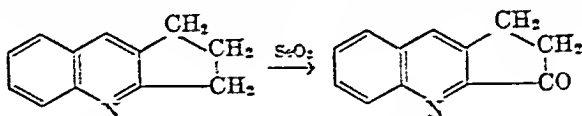
Heterocyclic compounds are attacked also by selenium dioxide at an activated methyl or methylene group. Such groups in pyridine or quinoline derivatives are oxidized to either aldehyde or carboxyl groups. For example, 2-picoline⁴⁵ gives a mixture of picolinic acid and 2-pyridinecarboxaldehyde. 2,6-Lutidine⁴⁶ yields dipicolinic acid, and



2,3,8-trimethylquinoline⁴⁷ is converted in 82% yield to 3,8-dimethylquininaldehyde. The conversion of 5,6-benzo-7-azahydrindene⁴⁸ to a keto

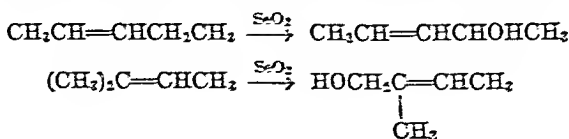


derivative illustrates the oxidation of an activated methylene group in a heterocyclic molecule. Selenium dioxide appears to show a greater



tendency to form acid derivatives with the nitrogen-containing heterocyclic compounds than with other substances.

The oxidation of olefinic compounds by selenium dioxide has led to a number of interesting and valuable results. Many of the materials available by this method are obtained only with considerable difficulty by other means. The simple olefins do not undergo oxidation at the α -methylene carbon atom; however, olefins which contain at least five carbon atoms behave normally. 2-Pentene^{42,43} is oxidized to 2-penten-4-ol, and 2-methyl-2-butene^{42,43} yields 2-methyl-2-buten-1-ol. The be-



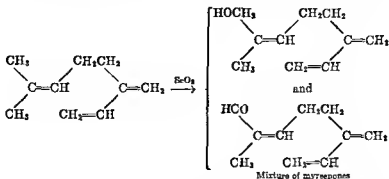
⁴⁵ Borsche and Hartmann, *Ber.*, 73, 839 (1940).

⁴⁶ Henze, *Ber.*, 67, 750 (1934).

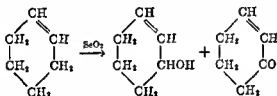
⁴⁷ Burger and Modlin, *J. Am. Chem. Soc.*, 62, 1079 (1940).

⁴⁸ Riley and Friend, *J. Chem. Soc.*, 1922, 2242.

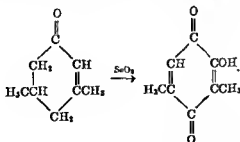
havior of myrcene⁴⁹ shows that selenium dioxide is capable of taking an olefin beyond the alcohol stage.



Cyclic olefins behave like aliphatic olefins. Cyclohexene^{18, 50, 51} can be oxidized to 1-cyclohexen-3-ol (50%) and cyclohexenone (6%).



3,5-Dimethyl-Δ²-cyclohexenone⁵² is converted to 3-hydroxy-2,6-dimethylquinone, which indicates that oxidation has occurred first at the



methylene group α to the double bond. This does not agree with the usual conception that the carbonyl group exerts the greater activating

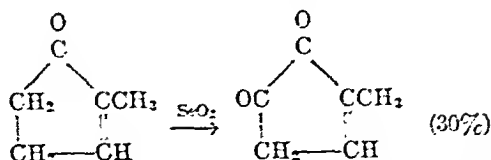
⁴⁹ Delaby and Dupin, *Bull. soc. chim. France*, [5] 8, 931 (1938); *Atté X^e congr. intern. chim.*, 3, 120 (1939) [*C.A.*, 33, 5194 (1939)].

⁵⁰ Schwenk and Borgwardt, *Ger. pat.* 584,373 (*Chem. Zentr.*, 1933, II, 3431).

⁵¹ Arbusov, Zelinskii, and Shulkin, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 1945, 163 [*C.A.*, 40, 3409 (1946)].

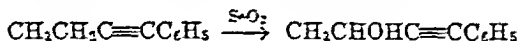
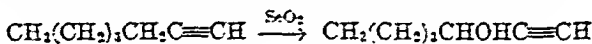
⁵² Dane and Schmitt, *Ann.*, 535, 196 (1938).

effect, as it does in 2-methyl- Δ^2 -cyclopentenone.²³ Cauquil²⁴ has re-

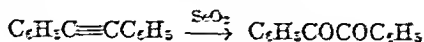


ported that pulegone is oxidized by selenium dioxide in the presence of ethyl alcohol to a mixture of 1-methyl-4-isopropylidene-2,3-cyclohexanedione, 1-methyl-4-isopropylidene-2,3,5-cyclohexanetrione, 1-methyl-2-ethoxy-4-isopropylidene-5-(or 6-)cyclohexen-3-one, and 1-methyl-4-isopropylidene-6-ethoxy-5-(or 6-)cyclohexene-2,3-dione. These results show the effect of activation of different methylene groups by a carbonyl group and an ethylenic linkage.

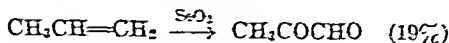
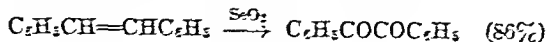
Simple acetylenic hydrocarbons behave similarly to olefins. Both 1-heptyne²⁵ and ethylphenylacetylene²⁶ are oxidized at the α -methylenic carbon atom to give 3-hydroxy-1-heptyne (27%) and 1-phenyl-3-hydroxy-1-butyne (25%) respectively. The ability of selenium dioxide



to bring about direct oxidation at a double or triple bond is illustrated by acetylenes which possess no activated methylene groups. Diphenylacetylene²⁷ is oxidized to benzil in 35% yield. Stilbene^{28,29} and the



lower olefins^{30,31} exhibit the same type of reaction.



Selenium dioxide is capable of producing a still different type of oxidation whereby oxygen does not enter the final product of the reaction. The dehydrogenating action of selenium dioxide has been observed in systems where two carbon atoms possessing hydrogen atoms are

²³ Dane, Schmitt, and Rantenstrauß, *Ann.*, 532, 29 (1937).

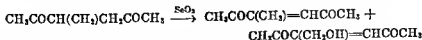
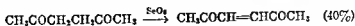
²⁴ Cauquil, *Compt. rend.*, 203, 1156 (1936).

²⁵ Truchet, *Compt. rend.*, 195, 705 (1933).

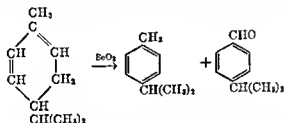
²⁶ Truchet, *Compt. rend.*, 195, 1613 (1933).

²⁷ Imperial Chem. Ind., Fr. pat. 734,537 [*C.A.*, 27, 999 (1933)], Ger. pat. 574,162 [*C.A.*, 27, 3456 (1933)].

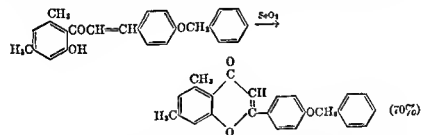
between two activating groups. 1,4-Diketones, such as 2,5-hexanedione^{38,39} and 3-methyl-2,5-hexanedione,³⁹ are changed to olefins.



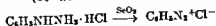
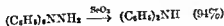
In the last reaction both dehydrogenation and oxidation have occurred. A similar dehydrogenation has been observed with certain terpenes. α -Phellandrene^{40,41} is converted to a mixture of cymene and cumaldehyde.



Selenium dioxide also brings about a number of other reactions. For instance, substituted chalcones⁴²⁻⁴⁵ are converted in good yields to flavones. Diphenylhydrazine⁴⁶ yields diphenylamine, and phenyl-



hydrazine derivatives⁴⁶ are dehydrogenated to diazonium salts. Numer-



³⁸ Armstrong and Robinson, *J. Chem. Soc.*, 1934, 1650.

³⁹ Goldberg and Müller, *Helv. Chim. Acta*, **21**, 1699 (1938).

⁴⁰ Borgwardt and Schwenk, *J. Am. Chem. Soc.*, **56**, 1185 (1934).

⁴¹ Hirayama, *J. Chem. Soc. Japan*, **59**, 67 (1938) [*C.A.*, **32**, 4969 (1938)].

⁴² Bargellini, *Atti X^e Congr. intern. chim.*, **3**, 32 (1939) [*C.A.*, **34**, 1018 (1940)].

⁴³ Bargellini and Marini-Bettolo, *Gazz. chim. Ital.*, **70**, 170 (1940).

⁴⁴ Chakravarti and Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939) [*C.A.*, **34**, 4735 (1940)].

⁴⁵ Mahal and Venkataraman, *J. Chem. Soc.*, 1936, 569.

⁴⁶ Postowsky, Lugowkin, and Mandryk, *Ber.*, **59**, 1913 (1930).

ergosterol derivatives, react readily at the temperature of the water bath. A third class, which includes nearly all the derivatives of cholesterol examined, does not react under these conditions, but reaction generally takes place at 100° in acetic acid or nitrobenzene.

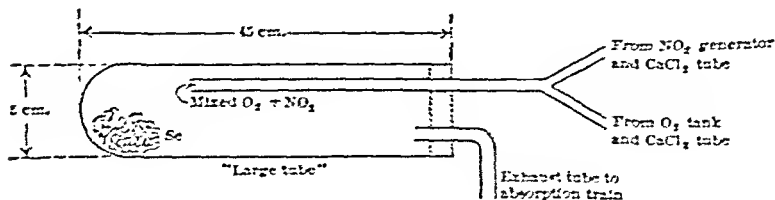
Most selenium dioxide oxidations can be carried out without the use of excessive temperatures. They are usually run at the boiling point of the solvent, and the commonly used solvents boil in the neighborhood of 100°. However, the oxidation of aromatic hydrocarbons, some dehydrogenation reactions, and the direct oxidation of double bonds appear to require higher temperatures. An interesting effect of temperature has been observed during the oxidation of $\Delta^{9,10}$ -octahydronaphthalene⁵⁰ in acetic anhydride. At 0–5° the product of the reaction is $\Delta^{9,10}$ -octahydro-1-naphthol acetate; at 25–30°, $\Delta^{9,10}$ -octahydro-1-naphthol acetate and $\Delta^{9,10}$ -octahydro-1,5-naphthalenediol diacetate; at 70°, $\Delta^{9,10}$ -octahydro-1-naphthol acetate, $\Delta^{9,10}$ -octahydro-1,5-naphthalenediol diacetate, and 1,2,3,5,6,7-hexahydro-1,5-naphthalenediol diacetate; and at 120–124°, only 1,2,3,5,6,7-hexahydro-1,5-naphthalenediol diacetate.

The isolation of the oxidation products usually involves merely the filtration of the reaction mixture to remove metallic selenium, distillation of the solvent, and then either crystallization or distillation of the residue. Only small amounts of selenium contaminate the residue if the usual procedure of employing the calculated amount of selenium dioxide is followed and the reaction is carried to completion. An excess of selenium dioxide can be removed by means of lead acetate, sulfur dioxide, or other reducing agents.

EXPERIMENTAL PROCEDURES

Preparation of Selenium Dioxide

A. By Combustion of Selenium in Oxygen and Nitrogen Dioxide.⁵¹ The apparatus used is shown in the figure. One hundred grams of selenium is placed in the closed end of the tube, and nitrogen dioxide and



⁵⁰ Campbell and Harris, *J. Am. Chem. Soc.*, **63**, 2721 (1941).

⁵¹ Niles, *Inorganic Synthesis*, **1**, 117 (1939).

oxygen, dried over calcium chloride, are introduced through the Y tube. Some regulation of the gas flow is necessary to secure the best results. The gases must be mixed thoroughly before coming in contact with the selenium. It is desirable to use separate drying tubes for each gas, as the nitrogen dioxide contains a great deal of moisture. If a stopcock is placed between the nitrogen dioxide dryer and the Y tube, the calcium chloride may be changed without interrupting the flow of oxygen or the heating.

When all the air and moisture have been displaced from the tube, the selenium is heated strongly with a Bunsen flame. A white deposit of selenium dioxide forms on the surface of the selenium but sublimes as soon as the temperature becomes sufficiently high.

At the same time, the remaining selenium melts to a viscous mass and eventually burns with a pale blue flame. The sublimate collects on the gas-delivery tube and on the sides of the large tube. The exit gases are bubbled through water and then sodium hydroxide solution to remove the oxides of nitrogen. After all the selenium has reacted, the contents of the tube are allowed to cool while oxygen still is passing through the apparatus and the selenium dioxide is removed.

A yield of 114 g. (80%) is obtained readily by this method. There is always some loss of selenium due, perhaps, to the formation of the suboxide. The presence of tellurium as an impurity in the selenium also decreases the yield. Tellurium remains behind, presumably in the form of the oxide which is not volatilized readily.

The selenium dioxide is obtained in the form of a snow-white product which may be kept in a tightly stoppered bottle for an indefinite period of time. It may turn pink on exposure to air as the result of reduction by dust.

B. By Oxidation of Selenium with Nitric Acid.²² One hundred milliliters of concentrated nitric acid is placed in a casserole or evaporating dish which is set on a sand bath. Heat is applied to the bath, and 60 g. of crude selenium is added cautiously in small portions to the nitric acid. The selenium should be scattered over the surface of the acid, and the frothing should be allowed to subside after each addition. By the time the reaction is completed, the sand bath should be at a temperature sufficient to start evaporation. Heating is continued until the residue appears dry. Care must be taken during the evaporation and subsequent cooling to keep the product broken up in order to avoid the formation of a hard, compact mass.

The residue is purified either by a wet treatment or by sublimation according to the procedure of Lenher.²³

²² Baker and Maxson, *Inorganic Syntheses*, **1**, 119 (1939).

²³ Lenher, *Am. Chem. J.*, **20**, 355 (1898).

Wet Purification. The residue is treated with enough water to bring the selenium dioxide into solution, and, after filtration, 10 ml. of concentrated hydrochloric acid is added. A slow stream of sulfur dioxide is passed into the solution until heat is no longer evolved. This requires from two to five hours. Red selenium is deposited, but it changes to a pasty gray form which becomes brittle on standing for a few hours. This change is accelerated by boiling.

The selenium is removed by filtration, ground in a mortar, washed free of acid, dried, and finally heated over a Bunsen burner. After the mass has cooled, it is dissolved in concentrated nitric acid and evaporated as described previously. In order to ensure the complete removal of the nitric acid, the residue is dissolved in 75 ml. of water and evaporated again. The yield of white selenium dioxide is about 76 g. (90%).

Purification by Sublimation. The crude selenium dioxide, which may be contaminated with copper and other heavy metals present in the selenium, is pulverized and placed in an evaporating dish. The selenium dioxide is moistened with a small amount of nitric acid, and two nested funnels are inverted over the evaporating dish (a plug of glass wool is placed in the neck of the larger funnel). The dish is heated with an open flame, and the selenium dioxide condenses in long needle-like crystals on the walls of the funnels; m.p. 340°.

The results observed by Kaplan⁵⁴ during the oxidation of methylquinolines are of interest. He found that selenium dioxide, freshly prepared by the action of nitric acid on metallic selenium, whether used directly or purified by sublimation, gave good yields of quinolinealdehydes consistent with those reported originally by Kwartler and Lindwall.⁵⁵ However, selenium dioxide which was prepared in the same manner but allowed to stand for several months before use afforded poor yields of the aldehydes; these yields were not improved by sublimation of such aged selenium dioxide at the time of use. On the other hand, if the selenium dioxide was sublimed immediately after preparation and stored, the loss of effectiveness in a given length of time was less marked than with the unsublimed material. The change that occurred in the selenium dioxide was not determined.

Preparation of Phenylglyoxal⁵⁶

In a 1-l. three-necked round-bottomed flask, fitted with a liquid-sealed stirrer and a reflux condenser, are placed 60 ml. of dioxane, 111 g. (1

⁵⁴ Kaplan, *J. Am. Chem. Soc.*, **63**, 2654 (1941).

⁵⁵ Kwartler and Lindwall, *J. Am. Chem. Soc.*, **59**, 524 (1937); Clemo and Hoggarth, *J. Chem. Soc.*, 1939, 1241.

⁵⁶ Riley and Gray, *Org. Syntheses*, **15**, 67 (1935).

mole) of selenium dioxide, and 20 ml. of water. The mixture is heated to 50–55° and stirred until the solid has gone into solution. Then 120 g. (1 mole) of acetophenone is added in one lot and the resulting mixture is refluxed with continued stirring for four hours. The hot solution is decanted from the precipitated selenium, and the dioxane and water are removed by distillation through a short column. The phenylglyoxal is distilled under diminished pressure from a 250-ml. Claisen flask, and the fraction boiling at 95–97°/25 mm. is collected. The yield is 93–96 g. (69–72%).

The aldehyde sets to a stiff gel on standing, probably as a result of polymerization. It may be recovered without appreciable loss by distillation. Phenylglyoxal may also be preserved in the form of the hydrate, which is prepared conveniently by dissolving the yellow liquid in 3.5–4 volumes of hot water and allowing crystallization to take place.

Preparation of 3,8-Dimethylquinoline-2-aldehyde ⁴⁷

A solution of 5 g. of 2,3,8-trimethylquinoline and 3.5 g. of selenium dioxide in 40 ml. of ethanol is boiled under reflux for six hours, and the precipitated selenium is filtered from the hot solution. The filtrate is concentrated, and 3.3 g. of the aldehyde is collected in the form of straw-colored needles. A reddish solid is precipitated by the addition of water to the mother liquor. It is removed by filtration and dissolved in 10 ml. of benzene, and the solution is shaken with 30 ml. of a saturated solution of sodium bisulfite for one hour. The crystalline addition product is filtered, washed with ether, and decomposed with dilute aqueous sodium carbonate. Another 1.2 g. of the aldehyde is obtained in this manner; the total yield is 82%. The aldehyde is purified by distillation under 1 mm. pressure followed by recrystallization from ethanol. It forms long colorless needles; m p., 107–108°.

Preparation of *cis*- Δ^5 -3,4-Cholestenediol ⁴⁷

A solution of 25 g. (0.22 mole) of selenium dioxide in 10 ml. of water and 500 ml. of acetic acid is warmed to 80° and mixed rapidly with a solution of 50 g. (0.13 mole) of cholesterol in 250 ml. of benzene which has been warmed also to 80°. The mixture immediately turns yellow and then red; it is refluxed on a steam bath for one hour. One hundred grams of sodium acetate is added, and, after heating for a few minutes, the black modification of selenium is deposited and removed by filtration. The filtrate is poured into 1 l. of half-saturated salt solution. The

⁴⁷ Rosenheim and Starling, *J. Chem. Soc.*, 1937, 377.

benzene layer is separated, washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue, which weighs 60 g., is suspended in 500 ml. of petroleum ether (b.p. 40–50°), allowed to settle in a tall cylinder, and washed twice by decantation with the same solvent. The crude, creamy-white product (26 g.), m.p., 174–175°, is crystallized once from acetone (Norit) and then from 85% ethanol. There is obtained 20 g. (39%) of the *cis*-diol in inch-long, monoclinic needles; m.p. 176–177°.

Preparation of Ninhydrin ⁹³

In a 2-l. three-necked flask fitted with a reflux condenser and a mechanical stirrer is placed 55 g. (0.5 mole) of sublimed selenium dioxide dissolved in 1.2 l. of dioxane and 25 ml. of water. The stirrer is started, and the solution is heated to approximately 60–70°. The flame is withdrawn, 73 g. (0.5 mole) of crude 1,3-diketohydrindene is added, and the resulting mixture is refluxed for six hours. A solid separates during this period and is filtered while the mixture is still hot. The filtrate is transferred to a distilling flask, and three-fourths of the dioxane is distilled. Between 400 and 500 ml. of water is added, and the solution is boiled to coagulate the tarry precipitate, which then is removed by filtration. The filtrate is concentrated by distillation to approximately 250 ml. and filtered. The filtrate is boiled with 1 g. of Norit, filtered again, concentrated to 125 ml., and allowed to stand at room temperature. The crude ninhydrin which crystallizes is filtered, the mother liquor concentrated, and a second crop of crystals obtained; the total yield of crude material is 36–38 g.

The impure ninhydrin is contaminated with a trace of selenious acid which acts as a bleaching agent and prevents the formation of the characteristic blue color reaction with α -amino acids. Crystallization from hot water with the aid of Norit furnishes 28–31 g. (31–35%) of long, colorless prisms of pure ninhydrin which gives none of the customary tests for selenium and produces the characteristic color reaction with α -amino acids. The purified product loses water of hydration and turns red between 125° and 130°, and finally it melts with decomposition at 241–243°.

SURVEY OF SELENIUM DIOXIDE OXIDATIONS

The following tables list the compounds which have been treated with selenium dioxide. The literature has been surveyed up to and including the August, 1947, *Chemical Abstracts*.

⁹³ Teeters and Shriner, *J. Am. Chem. Soc.*, 55, 3026 (1933).

The compounds are divided into the following sections, which are arranged in alphabetical order: *Acids and Acid Derivatives*, *Alcohols*, *Aldehydes*, *Hydrocarbons*, *Ketones*, *Nitrogen-Containing Compounds*, *Phenolic Compounds*, *Steroids*, *Sulfur-Containing Compounds*, *Terpenes*, and *Miscellaneous*. These have been broken down further into a number of sub groups which are listed below. The attempt has been made to place compounds which contain more than one functional group according to the most dominant characteristic.

Since it has often been necessary to depend upon abstracts rather than the original articles, omissions of items such as the solvents used or the yields obtained do not always mean that the data have not been published.

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ACIDS AND ACID DERIVATIVES

| Compound Treated | Solvent | Product | Yield % | Reference * |
|-------------------------------------|-------------------------------------|--|---------|-------------|
| ACIDS | | | | |
| 3,4-Dimethoxyhomophthalic acid | Xylene | 2,3-Dimethoxyphthalonic acid | — | 43 |
| 4,6-Dimethoxyhomophthalic acid | Xylene | m-Opianic acid | — | 42 |
| 5,6-Dimethoxyhomophthalic acid | Xylene | p-Opianic acid | — | 42 |
| Homophthalic acid | Xylene | Phthalonic acid | 80 | 42 |
| Hydrocyanic acid | (CH ₃ CO) ₂ O | Selenium + unidentified products | — | 86 |
| Lauric acid | None | Undecene | — | 38 |
| Leucine | None | C ₈ H ₁₇ NO | — | 38 |
| Levulinic acid | CH ₃ CO ₂ H | Not isolated | — | 15 |
| 5-Methoxyhomophthalic acid | Xylene | 4-Methoxyphthalonic acid | — | 43 |
| 4,5-Methylenedioxyhomophthalic acid | Xylene | 4,5-Methylenedioxyphthalonic acid | — | 44 |
| Myristic acid | None | Tridecene | — | 38 |
| Palmitic acid | None | Pentadecene | — | 38 |
| Phenoxyacetic acid | H ₂ O | Diphenoxyacetic acid selenoxide | — | 84 |
| Propionic acid | — | Pyruvic acid | — | 41 |
| Pyruvic acid | CH ₃ CO ₂ H | Not isolated | — | 15 |
| Stearic acid | None | Heptadecene | — | 38 |
| Thiocyanic acid | H ₂ O | Se + CO ₂ + SO ₄ ²⁻ + H ⁺ + NH ₄ ⁺ | — | 99 |

ANHYDRIDES

| | | | | |
|---|-------------------------------------|---|----|------------|
| Acetic anhydride | None | Glyoxylic acid | 17 | 35, 86, 87 |
| 1,2-Dimethyl-1,2,3,6-tetrahydrophthalic anhydride | (CH ₃ CO) ₂ O | 1,2-Dimethyl-6-acetoxy-1,2,3,6-tetrahydrophthalic anhydride | — | 100 |

* References 93-99 are on pp. 382-387.

ACIDS AND ACID DERIVATIVES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--|----------------------------------|---|--------------|-------------|
| <i>ESTERS</i> | | | | |
| Diethyl cyclopentane-1,3-dione-2,5-dicarboxylate | <i>Dioxane</i> | Diethyl cyclopentane-1,3,4-trione-2,5-dicarboxylate | — | 101 |
| Diethyl glutaconate | $\text{CH}_3\text{CO}_2\text{H}$ | Diethyl ketoglutaconate | — | 102 |
| Diethyl malate | None | Diethyl diketosuccinate + diethyl fumarate + ethyl hydrogen mesoxalate + oxalic acid + malic acid + ethyl hydrogen malate | — | 17 |
| Diethyl malonate | None | Diethyl mesoxalate + monoethyl ester of mesoxalic acid + diethyl oxalate | 32 | 10, 32, 33 |
| Diethyl β -ketoglutarate | None | Ethyl α,β -diketobutyrate | — | 17 |
| Diethyl succinate | None | Diethyl diketosuccinate + diethyl fumarate + ethyl hydrogen fumarate | — — 40 | 33 |
| Diethyl tartrate | None | Diethyl ketohydroxysuccinate | 11 | 103 |
| Dimethyl tartrate | None | Dimethyl fumarate | — | 103 |
| Ethyl acetoacetate | Xylene | Ethyl α,β -diketobutyrate | 35 | 32 |
| Ethyl lactate | None | Ethyl pyruvate + $\text{OHCOCO}_2\text{C}_2\text{H}_5$ or $\text{OHCCHCO}_2\text{C}_2\text{H}_5$ | — | 103 |
| | | OH | | |
| Ethyl β -methylcinnamate | <i>Dioxane</i> | β -Phenyl- Δ^4 -butenolide | — | 104 |
| Ethyl β -phenylpropionate | None | Cinnamic acid | 8 | 17 |
| Tetrahydrofurfuryl acetate | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 105 |

* References 99-324 are on pp 333-336.

ALCOHOLS

| Compound Treated | Solvent | Product | Yield % | Reference * |
|-------------------------------|---|--------------------------|---------|-------------|
| Benzyl alcohol | None | Benzaldehyde | 100 | 33 |
| n-Butyl alcohol | None | Ethylglyoxal | Trace | 33 |
| 2,2-Dimesitylethanol | — | Mesityl | — | 106 |
| Ethyl alcohol | None | Glyoxal | 41 | 7, 33 |
| Isobutyl alcohol | — | Diisobutyl selenite | — | 7 |
| Methanol | — | Dimethyl selenite | — | 7 |
| α -Methylallyl alcohol | $(C_2H_5)_2O$, C_2H_5OH , or dioxane | α -Methylacrolein | 62 | 107 |
| β -Methylallyl alcohol | Hexyl alcohol or dioxane | β -Methylacrolein | 50-60 | 103 |
| n-Propyl alcohol | None | Methylglyoxal | Trace | 7, 33 |
| Tetrahydrofurfuryl alcohol | None | No reaction | — | 109 |

ALDEHYDES

| | | | | |
|--------------------|-----------------------------------|---|----|-----------|
| Acetaldehyde | None | Glyoxal | 90 | 4, 11, 19 |
| n-Butyraldehyde | None | Ethylglyoxal | 45 | 4, 11, 19 |
| Cinnamaldehyde | None | Hydrocinnamic acid | — | 33 |
| Crotonaldehyde | CH_3OH | β -Methoxy- α -keto- butyraldehyde | 19 | 87 |
| | $(CH_3CO)_2O$ | β -Acetoxy- α -keto- butyraldehyde | — | 87 |
| | H_2O or CH_3CO_2H | Polymeric β -hydroxy- α -ketobutyralde- hyde | — | 87 |
| | $(CH_3CO)_2O \div$ CH_3CO_2H | Diacetate of croton- aldehyde | — | 87 |
| Heptaldehyde | CH_3CO_2H | Not isolated | — | 11 |
| Homopiperonal | — | 3,4-Methylenedioxy- phenylglyoxal | — | 110 |
| Isobutyraldehyde | CH_3CO_2H | Not isolated | — | 11 |
| Isovaleraldehyde | CH_3CO_2H | Not isolated | — | 11 |
| Paraldehyde | Dioxane \div CH_3CO_2H | Glyoxal† | 74 | 111 |
| Phenylacetaldehyde | None | Phenylglyoxal | 35 | 4 |
| Propionaldehyde | None | Methylglyoxal | 30 | 4, 11, 19 |

* References 99-224 are on pp. 352-356.

† Isolated as the bisulfite addition product.

HYDROCARBONS

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---------------------------|---|---|---------|------------------|
| ALKANES | | | | |
| Ethane | None | Glyoxal + acetic acid + carbon dioxide | — | 48 |
| OLEFINS | | | | |
| Ethylene | None | Glyoxal | 82 | 48, 57, 112, 113 |
| 1-Hexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-Hexen-1-ol acetate + 1-hexen-3-ol acetate | — | 16 |
| 2-Methyl-2-butene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-Methyl-2-buten-1-ol acetate | — | 16, 48 |
| | | Isoprene + tiglaldehyde + tiglic alcohol | — | |
| 2-Methyl-2-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-Methyl-2-penten-1-ol acetate | — | 16 |
| 3-Methyl-2-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 3-Methyl-3-penten-2-ol acetate + 2-ethyl-2-buten-1-ol acetate | — | 16 |
| 3-Methyl-3-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 3-Methyl-3-penten-2-ol acetate | — | 16 |
| 3-Nonene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | Mixture of acetates of nonenols | — | 16 |
| 4-Nonene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | Mixture of acetates of nonenols | — | 16 |
| Olefins | — | Olefin oxides, glycols, etc. | — | 114 |
| 2-Pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-Penten-4-ol acetate | — | 16, 48 |
| 2,3-Dimethyl-3-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-Isopropyl-2-buten-1-ol acetate | — | 16 |
| 3-Phenyl-3-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 3-Phenyl-3-penten-2-ol acetate | — | 16 |
| Propylene | None | Methylglyoxal | 19 | 48, 57 |
| Stilbene | None | Benzil | 86 | 17, 36 |
| Styrene | — | No reaction | — | 48 |
| 2,2,3-Trimethyl-3-pentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2-tert-Butyl-2-buten-1-ol acetate | — | 16 |

* References 99-324 are on pp. 353-356.

HYDROCARBONS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--------------------------------------|------------------------------|--|---------|-------------|
| DIOLEFINS | | | | |
| 1,6-Dibiphenylene-1,5-hexadiene | $C_2H_5OCH_3 \div CH_3CO_2H$ | 1,6-Dibiphenylene-hexatriene | — | 115 |
| 1,3-Pentadiene | — | 3-Pentene-1,2-diol | — | 116 |
| 1,1,6,6-Tetraphenyl-1,5-hexadiene | CH_3CO_2H | 1,1,6,6-Tetraphenyl-hexatriene | 50 | 115 |
| 1,1,5,5-Tetraphenyl-1,4-pentadiene | — | 1,1,2,2-Tetra-(β,β -diphenylvinyl)ethane | 60 | 117 |
| CYCLOOLEFINS | | | | |
| Cyclohexene | $CH_3CO_2H \div (CH_3CO)_2O$ | 1-Cyclohexen-3-ol acetate \div cyclohexenone | 50 6 | 16, 50, 51 |
| | $(CH_3)_2CO \div H_2O_2$ | <i>trans</i> -Cyclohexanediol | 45 | |
| Cyclopentadiene | — | Cyclopentene-3,4-diol | — | 116 |
| Cyclopentene | $(CH_3CO)_2O$ | Cyclopentenol acetate \div cyclopentendiol diacetate | — | 53 |
| Dihydro- α -dicyclopentadiene | CH_3OH | Methyl ether of dihydro- α -dicyclopentadien-3-ol | — | 88 |
| | C_2H_5OH | Ethyl ether of dihydro- α -dicyclopentadien-3-ol | 60 | 88 |
| | $C_5H_{11}OH$ | Amyl ether of dihydro- α -dicyclopentadien-3-ol | — | 88 |
| | $(CH_3CO)_2O$ | Dihydro- α -dicyclopentadien-3-ol acetate | 73 | 88 |
| Dihydronordicyclopentadiene | CH_3CO_2H | Dihydro-exo-dicyclopentadien-3-ol acetate | 33 | 118 |

* References 93-324 are on pp. 382-385.

HYDROCARBONS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---------------------------------------|---|---|---------|-------------|
| CYCLOOLEFINS—Continued | | | | |
| Dihydro- α -tricyclopentadiene | $(\text{CH}_3\text{CO})_2\text{O}$ | Dihydro- α -tricyclopentadien-3-ol acetate | 80 | 88 |
| Dihydro- β -tricyclopentadiene | $(\text{CH}_3\text{CO})_2\text{O}$ | Dihydro- β -tricyclopentadien-3-ol acetate | 61 | 88 |
| 1,2-Dimethylcyclohexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2,3-Dimethyl-1,3-cyclohexadiene + <i>o</i> -xylene | 70 | 16, 119 |
| 1,6-Dimethylcyclohexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 2,3-Dimethyl-1,3-cyclohexadiene + <i>o</i> -xylene | — | 16, 119 |
| 1-Ethylcyclohexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 1-Ethylcyclohexen-6-ol acetate | 23 | 16 |
| 1-Ethylcyclopentene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 1-Ethylcyclopenten-5-ol acetate | 10 | 16 |
| 1-Methylcyclohexene | $\text{C}_2\text{H}_5\text{OH}$ | 1-Methylcyclohexen-6-ol + 1-methylcyclohexen-6-one | 33, 27 | 89, 120 |
| | H_2O | 1-Methylcyclohexen-6-one | 90 | 89 |
| | $\text{CH}_3\text{CO}_2\text{H}$ | 1-Methylcyclohexen-6-ol acetate | 40 | 89 |
| 3-Methylcyclohexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 6-Methylcyclohexen-3-ol acetate + 4-methylcyclohexen-3-ol + 1-methylcyclohexene + toluene | — | 16 |
| | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 6-Methylcyclohexen-3-ol acetate + 4-methylcyclohexen-3-ol acetate | — | 119 |
| 4-Methylcyclohexene | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 4-, 5-, and 6-Methylcyclohexen-3-ol acetates | — | 16 |
| | $\text{CH}_3\text{CO}_2\text{H} + (\text{CH}_3\text{CO})_2\text{O}$ | 6-Methylcyclohexen-3-ol acetate + 4-methylcyclohexen-3-ol acetate + 4-methylcyclohexen-1-ol acetate | — | 119 |

* References 99-374 are on pp. 352-356.

HYDROCARBONS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

CYCLOOLEFINS—*Continued*

| | | | | |
|---|--|--|------------|-----|
| 1-Methylcyclopentene | (CH ₃ CO) ₂ O | 1-Methylcyclopenten-5-ol acetate | — | 53 |
| 1-Methyl-2- <i>sec</i> -isooctyl-1 (?) cyclopentene | C ₄ H ₉ OH | Not isolated | — | 121 |
| 9-Methyloctahydronaphthalene | (CH ₃ CO) ₂ O | <i>cis</i> -9-Methyloctahydro-3-naphthol acetate | 17 | 122 |
| $\Delta^{9,10}$ -Octahydronaphthalene | (CH ₂ CO) ₂ O (0-5°) | $\Delta^{9,10}$ -Octahydro-1-naphthol acetate | 65 | 90 |
| | (CH ₂ CO) ₂ O (25-30°) | $\Delta^{9,10}$ -Octahydro-1-naphthol acetate + $\Delta^{9,10}$ -octahydro-1,5-naphthalenediol diacetate | 35 12.5 | 90 |
| | (CH ₃ CO) ₂ O (70°) | $\Delta^{9,10}$ -Octahydro-1-naphthol acetate + $\Delta^{9,10}$ -octahydro-1,5-naphthalenediol + 1,2,3,5,6,7-hexahydro-1,5-naphthalenediol diacetate | 17 | 90 |
| | (CH ₃ CO) ₂ O (120-124°) | 1,2,3,5,6,7-Hexahydro-1,5-naphthalenediol diacetate | — | 90 |
| 1,1,3,5-Tetramethyl-2,4-cyclohexadiene | CH ₃ CO ₂ H | 2,2,4,4-Tetramethyl-3,5-cyclohexadienone | — | 123 |
| 1,1,4-Trimethyl-3-cycloheptene | C ₂ H ₅ OH | 1,1,4-Trimethyl-3-cyclohepten-5-one + 1,1-dimethyl-3-cycloheptene-4-carboxaldehyde | — | 124 |

ACETYLENES

| | | | | |
|-----------------|------|--------------|---|---------|
| Acetylene | None | Glyoxal | 6 | 48, 125 |
| Phenylacetylene | None | Benzoic acid | — | 36 |

* References 50-324 are on pp. 352-354.

HYDROCARBONS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

ACETYLENES—Continued

| | | | | |
|--------------------|----------------------------------|-----------------------------|----|----|
| Diphenylacetylene | None | Benzil | 35 | 36 |
| 1-Phenyl-1-propyne | — | 1-Phenyl-3-hydroxy-1-butyne | 25 | 56 |
| 1-Heptyne | C ₂ H ₅ OH | 3-Hydroxy-1-heptyne | 27 | 55 |
| 1-Octyne | C ₂ H ₅ OH | 3-Hydroxy-1-octyne | — | 55 |

AROMATIC HYDROCARBONS

| | | | | |
|--------------------------|---|---|------------|--------|
| Acenaphthene | None | Acenaphthylene + <i>cis</i> -acenaphthene glycol + <i>trans</i> -acenaphthene glycol | 25 16 | 126 |
| | CH ₃ CO ₂ H | Acenaphthylene + acenaphthylene glycol + polyacenaphthylene + dinaphthylene-cyclobutane | — | 127 |
| Anthracene | None | Anthraquinone | 76 | 36 |
| | C ₆ H ₅ NO ₂ | Anthraquinone | 73 | 17, 36 |
| | H ₂ O | Anthraquinone | 70 | 127a |
| Benzene | None | Not isolated | — | 128 |
| Bibenzyl | None | Benzil + stilbene | 33 17.5 | 17 |
| | | Chrysosfluorenone | 80 | 37 |
| Chrysosfluorene | H ₂ O | 1,2,5,6-Dibenzosfluorenone | 39 | 37 |
| 1,2,5,6-Dibenzosfluorene | H ₂ O | 1,2,7,8-Dibenzosfluorenone | 38 | 129 |
| 1,2,7,8-Dibenzosfluorene | H ₂ O | 3,4,5,6-Dibenzosfluorenone | — | 129 |
| 3,4,5,6-Dibenzosfluorene | H ₂ O | 1,2,8,9-Dibenzopentacene-6,13-quinone | — | 130 |
| 1,2,8,9-Dibenzopentacene | C ₆ H ₅ NO ₂ | Anthracene | 60 | 127a |
| 9,10-Dihydroanthracene | CH ₃ CO ₂ H | | | |

* References 99-324 are on pp. 352-355.

HYDROCARBONS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

AROMATIC HYDROCARBONS—*Continued*

| | | | | |
|------------------------|--------------|--------------------------|----|------------|
| 7,16-Dihydroheptacene | $C_6H_5NO_2$ | 7,16-Heptacene-quinone | — | 39 |
| 6,15-Dihydrohexacene | $C_6H_5NO_2$ | 6,15-Hexacene-quinone | — | 39 |
| Diphenylmethane | None | Benzophenone | 87 | 34, 35, 36 |
| Fluorene | H_2O | Fluorenone | 65 | 36, 37 |
| Hexahdropyrene | CH_3CO_2H | Pyrene | 60 | 127a |
| Indene | — | Hydrindene + C_3H_{10} | — | 38 |
| 9-Methyldecalin | — | No reaction | — | 131 |
| as-Octahydroanthracene | H_2O | Anthraquinone | — | 127a |
| s-Octahydroanthracene | H_2O | Anthraquinone | — | 127a |
| Phenanthrene | None | Phenanthraquinone | 3 | 17, 36 |
| Polybenzyl | Dioxane | No reaction | — | 132 |
| Toluene | — | Benzoic acid | — | 41 |
| Triphenylmethane | None | Triphenylcarbinol | 15 | 35 |

SUBSTITUTED AROMATIC HYDROCARBONS

| | | | | |
|-------------------------------------|-----------------------|---------------------------------------|----|--------|
| Benzyl chloride | None | Benzaldehyde | 49 | 35, 40 |
| 2,4-Dinitrotoluene | C_2H_5OH or dioxane | No reaction | — | 35 |
| p-Nitrobenzal bromide | None | p-Nitrobenzoic acid | — | 35 |
| p-Nitrobenzyl bromide | None | p-Nitrobenzaldehyde | 56 | 35 |
| 7(?) -Nitro-1,2,5,6-dibenzofluorene | H_2O | 7(?) -Nitro-1,2,5,6-dibenzofluorenone | — | 133 |
| p-Nitrotoluene | None | p-Nitrobenzoic acid | — | 35 |
| 2,4,6-Trinitrotoluene | C_2H_5OH or dioxane | No reaction | — | 35 |

KETONES

MONOKETONES

| | | | | |
|-----------------|---------|----------------|------|------------------------|
| Acetomesitylene | Dioxane | Mesitylglyoxal | 82.5 | 134 |
| Acetone | None | Methylglyoxal | 60 | 4, 10, 12, 19, 135-135 |

* References 99-324 are on pp. 352-355.

KETONES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

MONOKETONES—Continued

| | | | | |
|--|-------------------------------------|--|---------|-----------------------------|
| Acetophenone | Dioxane | Phenylglyoxal | 70 | 4, 10, 13, 19, 96, 138, 139 |
| 9-Acetyloctahydroanthracene | Dioxane | Octahydro-9-anthracenecglyoxal hydrate | 83 | 140 |
| 2-Benzylbenzanthrone | None | 2-Benzoylbenzanthrone | — | 3 |
| Benzyl 4-biphenyl ketone | (CH ₃ CO) ₂ O | 4-Phenylbenzil | 95 | 20 |
| Benzyl 4-bromophenyl ketone | (CH ₃ CO) ₂ O | 4-Bromobenzil | 97 | 20 |
| Benzyl 4-chlorophenyl ketone | (CH ₃ CO) ₂ O | 4-Chlorobenzil | 98 | 20 |
| Benzyl duryl ketone | Dioxane | Phenyl duryl diketone | — | 141 |
| Benzyl isoduryl ketone | Dioxane | Phenyl isoduryl diketone | 81 | 142 |
| Benzyl mesityl ketone | (CH ₃ CO) ₂ O | 2,4,6-Trimethylbenzil | 97 | 20 |
| Benzyl methyl ketone | Dioxane | Phenyl methyl diketone | 60 | 13, 143 |
| Benzyl p-tolyl ketone | (CH ₃ CO) ₂ O | 4-Methylbenzil | 74 | 20 |
| Benzyl 2,4,6-triisopropylphenyl ketone | Dioxane | 2,4,6-Triisopropylphenyl phenyl diketone | 85 | 141, 144 |
| Benzyl 4-(o-xylyl) ketone | (CH ₃ CO) ₂ O | 3,4-Dimethylbenzil | 98 | 20 |
| Benzyl 4-(m-xylyl) ketone | (CH ₃ CO) ₂ O | 2,4-Dimethylbenzil | — | 20 |
| Benzyl p-xylyl ketone | (CH ₃ CO) ₂ O | 2,5-Dimethylbenzil | 89 | 20 |
| 3-Bromoacetomesitylene | Dioxane | 3-Bromomesityl-glyoxal | 65 | 145 |
| p-Bromoacetophenone | Xylene | p-Bromophenyl-glyoxal | 55 | 13, 146 |
| p-Bromobenzyl mesityl ketone | Dioxane | p-Bromophenyl mesityl diketone | 72 | 145 |
| 3-Bromo-5-nitroacetomesitylene | Dioxane | 3-Bromo-5-nitromesityl-glyoxal | 90 | 145 |
| 2-Butanone | None | Ethylglyoxal + biacetyl | 17 1 | 4, 10, 12, 19 |

* References 99-324 are on pp. 382-386.

KETONES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--|---|-------------------------------------|---------|-------------------|
| Monoketones—Continued | | | | |
| <i>p</i> -Chloroacetophenone | Xylene | <i>p</i> -Chlorophenylglyoxal | 64 | 13, 145 |
| Crotonophenone | Dioxane | No reaction | — | 147 |
| Cycloheptanone | C ₂ H ₅ OH | 1,2-Cycloheptanedione | — | 21 |
| Cyclohexanone | C ₂ H ₅ OH | 1,2-Cyclohexanedione | 45 | 4, 19, 120 148 |
| Cyclooctanone | C ₂ H ₅ OH | 8-Ethoxy-1,2-cyclooctanedione | — | 21 |
| Cyclopentanone | C ₂ H ₅ OH | 1,2-Cyclopentanedione | 7 | 4 |
| Desoxybenzoin | (CH ₃ CO) ₂ O | Benzil | 88 | 20 |
| 3,5-Dibromoisobutyrophenone | Dioxane | 3,5-Dibromoisobutyrophenylglyoxal | 41.5 | 149 |
| 3,5-Dimethyl-1,2-cyclohexanone | CH ₃ CO ₂ H | 3-Hydroxy-2,6-dimethylquinone | — | 52 |
| 2,4-Dimethyl-6-methoxyacetophenone | Dioxane | 2,4-Dimethyl-6-methoxyphenylglyoxal | — | 150 |
| 2,4-Dimethyl-3-pentanone | CH ₃ CO ₂ H | Not isolated | — | 10 |
| Diphenylacetoin | — | 1,4-Diphenyl-2,3-butanedione | — | 151 |
| 3,4-Diphenylcyclopentanone | Dioxane | 3,4-Diphenyl-3-cyclopentanone | — | 152 |
| 2,3-Diphenylcyclopentanone | Dioxane | No reaction | — | 153 |
| Drypene | Dioxane | 2,4-Diphenylfuran | 10 | 147 |
| <i>p</i> -Ethoxyacetophenone | Dioxane | <i>p</i> -Ethoxyphenylglyoxal | 40 | 154 |
| 3-Ethyl-5-hydroxy-6,7-dimethoxy-3,4-dihydro-1(2)-naphthalenone | CH ₃ CO ₂ H or C ₂ H ₅ OH | Red dye | — | 155 |
| 2-Heptanone | CH ₃ CO ₂ H | Not isolated | — | 14 |
| 4-Heptanone | CH ₃ CO ₂ H | Not isolated | — | 10 |
| 2-Hydroxy-4'-benzyloxy-4,6-dimethoxychalcone | C ₂ H ₅ OH | 4'-Benzyloxy-5,7-dimethoxyflavone | 70 | 65 |

* References 99-324 are on pp. 332-334.

KETONES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--|-----------------------------------|--|---------|-------------|
| MONOKETONES—Continued | | | | |
| 2-Hydroxy-4-benzoyloxy-phenyl styryl ketone | C ₆ H ₁₁ OH | 7-Benzoyloxyflavone | 34 | 156 |
| 2-Hydroxy-3-chloro-3',4'-dimethoxychalcone | C ₆ H ₁₁ OH | 8-Chloro-3',4'-dimethoxyflavone | — | 64 |
| 2-Hydroxy-5-chloro-3',4'-dimethoxychalcone | C ₆ H ₁₁ OH | 6-Chloro-3',4'-dimethoxyflavone | — | 64 |
| 2-Hydroxy-4-(β,γ -dihydroxypropoxy) phenyl styryl ketone | — | 7-(β,γ -Dihydroxypropoxy)flavone | — | 157 |
| 2-Hydroxy-4,5-dimethoxychalcone | C ₆ H ₁₁ OH | 6,7-Dimethoxyflavone | — | 63 |
| 2-Hydroxy-3,4-dimethoxycinnamylideneacetophenone | C ₆ H ₁₁ OH | 7,8-Dimethoxy-2-styrylchromone | — | 158 |
| 2-Hydroxy-3,4-dimethoxyfurfurylideneacetophenone | C ₆ H ₅ OH | 7,8-Dimethoxy-2-(2-furyl)chromone | — | 159 |
| 2-Hydroxy-4,5-dimethoxyfurfurylideneacetophenone | C ₆ H ₅ OH | 6,7-Dimethoxy-2-(2-furyl)chromone | — | 159 |
| 2-Hydroxy-4-methoxycinnamylideneacetophenone | C ₆ H ₁₁ OH | 7-Methoxy-2-styrylchromone | — | 153 |
| 2-Hydroxy-4-methoxyfurfurylideneacetophenone | C ₆ H ₁₁ OH | 7-Methoxy-2-(2-furyl)chromone | — | 159 |
| 2-Hydroxy-3-nitro-5-methyl-3',4'-dimethoxychalcone | C ₆ H ₁₁ OH | 6-Methyl-8-nitro-3',4'-dimethoxyflavone | — | 64 |
| o-Hydroxyphenyl styryl ketone | C ₆ H ₁₁ OH | Flavone | 42 | 156 |
| 2-Hydroxy-3,4,6,4'-tetramethoxychalcone | C ₆ H ₁₁ OH | 5,7,8,4'-Tetramethoxyflavone | — | 62 |
| 2-Hydroxy-4,5,4'-trimethoxychalcone | C ₆ H ₁₁ OH | 6,7,4'-Trimethoxyflavone | — | 63 |
| p-Iodoacetophenone | CH ₃ CO ₂ H | Not isolated | — | 13 |

* References 99-324 are on pp. 352-355.

KETONES—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|---|--|---------|-------------|
| <i>MONOKETONES—Continued</i> | | | | |
| 3'-Keto-4,6-dimethoxy-1,2-cyclopentenonaphthalene | CH ₃ CO ₂ H | 2',3'-Diketo-4,6-dimethoxy-1,2-cyclopentenonaphthalene | — | 160 |
| Ketotetrahydrobenzofluorene | Dioxane | No reaction | — | 161 |
| p-Methoxyacetophenone | CH ₃ CO ₂ H | Not isolated | — | 13 |
| p-Methylacetophenone | CH ₃ CO ₂ H | p-Methylphenylglyoxal | — | 13, 146 |
| 2-Methylbenzanthrone | H ₂ O | Benzanthrone-2-carboxaldehyde | — | 3 |
| 6-Methylbenzanthrone | H ₂ O | Benzanthrone-6-carboxaldehyde | — | 3 |
| 9-Methyl-meso-benzanthrone | H ₂ O | meso-Benzanthrone-9-carboxaldehyde + meso-benzanthrone-9-carboxylic acid | 24 | 162 |
| 10-Methyl-meso-benzanthrone | C ₆ H ₅ NO ₂ | meso-Benzanthrone-10-carboxaldehyde + meso-benzanthrone-10-carboxylic acid | 32 | 162 |
| 3-Methyl-2-butanone | CH ₃ CO ₂ H | Not isolated | — | 10 |
| 2-Methylcyclohexanone | C ₂ H ₅ OH | 3-Methyl- Δ^3 -1,2-cyclohexenedione | — | 21 |
| 3-Methylcyclohexanone | C ₂ H ₅ OH | 3-Methyl- Δ^3 -1,2-cyclohexenedione | — | 21 |
| 4-Methylcyclohexanone | C ₂ H ₅ OH | 4-Methyl-1,2-cyclohexanedione + 4-methyl-6-ethoxy- Δ^2 -cyclohexenone | — | 21 |
| Methyl cyclohexyl ketone | Dioxane | Cyclohexylglyoxal | 59 | 163 |
| 2-Methyl- Δ^2 -cyclopentenone | (CH ₃ CO) ₂ O | 3-Methyl- Δ^3 -1,2-cyclopentenedione | 30 | 53 |
| 3-Methyl-1-tetralone | C ₂ H ₅ OH | 2-Hydroxy-3-methyl-1,4-naphthoquinone | 45 | 164 |
| | | ÷ 3-methyl-1,2-naphthoquinone | — | |

* References 99-324 are on pp. 352-356.

KETONES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

MONOKETONES—Continued

| | | | | |
|--|---|--|----|--------------|
| 2-Methyl-1,1'-dinaphthyl ketone | H ₂ O | 2-Carboxy-1,1'-dinaphthyl ketone | 56 | 165 |
| 2-Methyl-1,2'-dinaphthyl ketone | H ₂ O | 2-Carboxy-1,2'-dinaphthyl ketone | 53 | 165 |
| 4-Methyl-1,2'-dinaphthyl ketone | C ₆ H ₄ NO ₂ | 4-Carboxy-1,2'-dinaphthyl ketone | — | 165 |
| Methyl α -naphthyl ketone | CH ₃ CO ₂ H | α -Naphthylglyoxal | 44 | 167 |
| Methyl β -naphthyl ketone | CH ₃ CO ₂ H | β -Naphthylglyoxal | 72 | 167 |
| 1-(2-Methylnaphthyl) 3',4',5'-trimethylphenyl ketone | H ₂ O | 1-(3',4',5'-Trimethylbenzoyl)-2-naphthoic acid acetoxy lactone | — | 168 |
| β -Naphthoflavanone | Xylene | β -Naphthoflavone | — | 166 |
| 3-Nitroacetomesitylene | Dioxane | 3-Nitromesitylglyoxal | 72 | 145 |
| <i>m</i> -Nitroacetophenone | CH ₃ CO ₂ H | Not isolated | — | 13 |
| <i>m</i> -Nitrobenzyl mesityl ketone | Dioxane | Mesityl <i>m</i> -nitrophenyl diketone | 81 | 145 |
| <i>p</i> -Nitrobenzyl mesityl ketone | Dioxane | Mesityl <i>p</i> -nitrophenyl diketone | 72 | 145 |
| 5-Nonanone | CH ₃ CO ₂ H | Not isolated | — | 10 |
| <i>trans</i> -Octahydro-2(1)-naphthalenone | C ₂ H ₅ OH | <i>trans</i> -Octahydro-2,3-naphthalenedione | 50 | 169, 170 |
| 2-Octanone | CH ₃ CO ₂ H | Not isolated | — | 10, 14 |
| 2-Pentanone | CH ₃ CO ₂ H | Not isolated | — | 10, 12 |
| 3-Pentanone | — | Methyl ethyl diketone | — | 10, 19 |
| 1-Phenylacetyl-3-nitro-4-methoxybenzene | (CH ₃ CO) ₂ O | 3-Nitro-4-methoxybenzil | 66 | 171 |
| Pinacolone | CH ₃ OH | <i>tert</i> -Butylglyoxal | 52 | 10, 172, 173 |
| Propiomesitylene | Dioxane | Methyl mesityl diketone | 42 | 145 |
| Propiophenone | C ₂ H ₅ OH | Methyl phenyl diketone | 50 | 4, 19 |
| Tetraphenylcyclopentadienone hydrate | CH ₃ CO ₂ H | 2,3,4-Triphenylbenzoylfuran | — | 174 |

* References 99-324 are on pp. 352-355.

KETONES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

MONOKETONES—Continued

| | | | | |
|--|------------------|---------------------------------------|------|----------|
| 3,3,5,6-Tetraphenyl-1-indanone | Dioxane | 3,3,5,6-Tetraphenyl-1,2-indandione | — | 152, 175 |
| 1- <i>p</i> -Toluoyl-2-methylnaphthalene | H ₂ O | 1- <i>p</i> -Toluoyl-2-naphthoic acid | 65 | 127a |
| 2,4,6-Triethylacetophenone | Dioxane | 2,4,6-Triethylphenylglyoxal | 78.5 | 176 |
| 2,4,6-Triisopropylacetophenone | Dioxane | 2,4,6-Triisopropylphenylglyoxal | 82 | 145 |

DIKETONES

| | | | | |
|--|---|--|----|-----|
| 1,9-Anthindandione | C ₆ H ₅ NO ₂ | Acceanthrenequinone | — | 177 |
| Benzoyl- β -isoduryloylmethane | Dioxane | Mesityl phenyl triketone + C ₂₆ H ₂₂ O ₄ Se | — | 83 |
| 1-Benzoyl-3,4,5,6-tetraphenyl-7-keto-1,2,3,6-tetrahydro-3,6-methanobenzene | CH ₃ CO ₂ H | No reaction | — | 178 |
| 2-Benzylanthraquinone | — | 2-Benzoylbenzanthrone | — | 3 |
| Bicyclo-[3.3.0]-2,6-octanedione | C ₂ H ₅ OH | Unstable oil | — | 179 |
| 1,3-Diacetylbenzene | Dioxane | <i>m</i> -Phenylenediglyoxal | — | 180 |
| 1,4-Diacetylbenzene | (CH ₃ CO) ₂ O | <i>p</i> -Phenylenediglyoxal | — | 181 |
| 1,5-Dibenzoyl-2,6-dimethylnaphthalene | C ₆ H ₅ NO ₂ | 1,5-Dibenzoylnaphthalene-2,6-dicarboxylic acid | — | 3 |
| 1,2-Dibenzoyl-1-propene | Dioxane | 2-Phenyl-4-benzoylfuran | 63 | 147 |
| Di-(β -isoduryloyl)-methane | Dioxane | Dimesityl triketone | — | 182 |
| 1,3-Diketohydrindene | Dioxane | Ninhydrin | 35 | 98 |
| 1,2-Dimesitylethylene glycol | Dioxane | Dimesityl triketone | 50 | 149 |

* References 99-324 are on pp. 382-385.

KETONES—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------|---------|---------|---------|-------------|
|------------------|---------|---------|---------|-------------|

DIKETONES—*Continued*

| | | | | |
|--|---|---|----|--------|
| Diphenylsuccindandione | CH ₃ CO ₂ H | C ₂₁ H ₁₆ O ₂ | 90 | 183 |
| 2,5-Hexanedione | H ₂ O | Δ ¹ -2,5-Hexenedione | 40 | 58, 59 |
| 3-Methyl-2,5-hexanedione | H ₂ O | 3-Methyl-Δ ¹ -2,5-hexenedione + 3-hydroxy-4-methyl-Δ ¹ -2,5-hexenedione | — | 59 |
| 1-Methyl-4-isopropylidene-2,3-cyclohexanedione | — | 1-Methyl-4-isopropylidene-2,3,5-cyclohexanetrione | — | 54 |
| 5-Methylnaphthoanthraquinone | — | Naphthoanthraquinone-5-carboxylic acid + naphthoanthraquinone-5-carboxaldehyde | — | 3 |
| 2-Methyl-1,4-naphthoquinone | C ₂ H ₅ OH | No reaction | — | 164 |
| 3-Methyl-1,2-naphthoquinone | C ₂ H ₅ OH | 2-Hydroxy-3-methyl-1,4-naphthoquinone | — | 164 |
| 1,8-Naphthindandione | C ₆ H ₅ NO ₂ | Acenaphthenequinone | — | 177 |
| 2-Nitro-1,4-diacetylbenzene | Dioxane | 2-Nitrophenylene-1,4-diglyoxal | — | 181 |
| 2,4-Pentanedione | C ₂ H ₅ OH | 2,3,4-Pentane-1,2,3-trione | 29 | 31 |
| 1-Phenyl-1,3-butanedione | C ₂ H ₅ OH | Unidentified | — | 31 |
| Triphenylcyclopentadienedione | Dioxane | C ₄₀ H ₂₀ O ₄ | — | 184 |

TRIKETONES

| | | | | |
|--------------------------------|---------|---------------------------|---|-----|
| 1,3,5-tris(Bromoacetyl)benzene | Dioxane | 1,3,5-Triglyoxalylbenzene | — | 181 |
|--------------------------------|---------|---------------------------|---|-----|

* References 99-324 are on pp. 352-353.

NITROGEN-CONTAINING COMPOUNDS

| Compound Treated | Solvent | Product | Yield % | Reference * |
|----------------------------|--|---|---------|-------------|
| AMINES | | | | |
| Aniline | CH ₃ OH | C ₇ H ₁₁ O ₂ NSe | — | 17 |
| | None | Violet compound | — | 128 |
| | C ₂ H ₅ OH + (C ₂ H ₅) ₂ O | Blue-black solid | — | 86 |
| Ethoxyphenylenediamine | H ₂ O | Ethoxypiaselenol | — | 185 |
| Ethylamine | — | Solid, m.p. 150° | — | 128 |
| Methylaniline | CH ₃ OH | Not isolated | — | 17 |
| 1,2-Naphthylenediamine | H ₂ O | Naphthopiaselenol | — | 186 |
| 1,8-Naphthylenediamine | H ₂ O | C ₂₀ H ₁₅ N ₄ Se | — | 187 |
| <i>o</i> -Phenylenediamine | H ₂ O | Piaselenol | — | 185 |
| <i>p</i> -Toluidine | CH ₃ OH | Not isolated | — | 17 |
| <i>o</i> -Tolylenediamine | HCl | Methylchloropiaselenol | — | 188 |
| <i>o</i> -Tolylenediamine | H ₂ O | Methylpiaselenol | — | 186 |
| 1,2,4-Triaminobenzene | H ₂ O | Aminopiaselenol | — | 185 |

HYDRAZINES

| | | | | |
|--|---|---|----------|---------|
| <i>p</i> -Bromophenylhydrazine hydrochloride | H ₂ O | <i>p</i> -Bromobenzenediazonium chloride | — | 66 |
| Diphenylhydrazine | C ₂ H ₅ OH | Diphenylamine | 94 | 66 |
| 1-Naphthylhydrazine hydrochloride | H ₂ O | 1-Naphthalenediazonium chloride | — | 66 |
| 2-Naphthylhydrazine hydrochloride | H ₂ O | 2-Naphthalenediazonium chloride | — | 66 |
| <i>m</i> -Nitrophenylhydrazine hydrochloride | H ₂ O | <i>m</i> -Nitrobenzenediazonium chloride | — | 66 |
| <i>p</i> -Nitrophenylhydrazine hydrochloride | H ₂ O | <i>p,p'</i> -Dinitrodiazobenzene + <i>p</i> -nitrodiazobenzeneimide | 46 32 | 66 |
| Phenylhydrazine | C ₂ H ₅ OH + H ₂ O | Not isolated | — | 86, 189 |
| Phenylhydrazine hydrochloride | H ₂ O | Benzenediazonium chloride | — | 66 |

* References 99-324 are on pp. 352-356.

NITROGEN-CONTAINING COMPOUNDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--|----------------------------------|---|-----------|-----------------------------|
| HETEROCYCLIC COMPOUNDS | | | | |
| Acridino | None | Dihydroacridine | — | 38 |
| 5,6-Benzo-7-aza-hydrindene | — | 1-Keto-5,6-benzo-7-azahydrindene | — | 45 |
| 9-Benzylacridine | Xylene | 9-Benzoylacridine | 60 | 190 |
| 2-(<i>o</i> -Carboxyphenyl)-4-keto-1,2,3,4-tetrahydroquinoline lactam | C ₆ H ₆ | 2-(<i>o</i> -Carboxyphenyl)-4-keto-1,4-dihydroquinoline lactam | — | 191 |
| 6,7-Dimethoxylepidine | Dioxane | 6,7-Dimethoxycinchoninaldehyde | 71 | 192 |
| 2,3-Dimethylbenzo(h)-quinoline | C ₂ H ₅ OH | 3-Methylbenzo(h)-quinoline-2-carboxylic acid | 20 | 193 |
| 2,4-Dimethylbenzo(h)-quinoline | C ₂ H ₅ OH | Benzo(h)quinoline-2,4-dicarboxylic acid | — | 193 |
| 1,3-Dimethyl-6,7-methylenedioxisoquinoline | Dioxane | 1,3-Dimethyl-6,7-methylenedioxisoquinolinaldehyde | — | 194 |
| 2-Ethyl-3-methylquinoline | Xylene | 3-Methylquininaldic acid | — | 46 |
| Ethyl 1-phenyl-5-keto-2-pyrazoline-3-carboxylate | — | Diethyl 1,1'-diphenyl-5,5'-dihydroxy-4,4'-bipyrazole-3,3'-dicarboxylate | — | 195 |
| 8-Ethylquinaldine | C ₂ H ₅ OH | 8-Ethylquininaldehyde | 90 | 196 |
| Hydroquinine | Xylene | Hydroquininone | 45 | 197 |
| Lepidine | Dioxane | Cinchoninaldehyde + 1,2-bis(4-quinolyl)-ethene | 58 100 | 94, 95, 198, 199, 200 |
| 2,6-Lutidine | Xylene | Dipicolinic acid | — | 46 |
| 6-Methoxylepidine | Xylene | Quininaldehyde | 56 | 95, 192 |
| 9-Methylacridine | Xylene | 9-Acridinecarboxaldehyde | — | 201 |
| 4-Methylbenzo(h)-quinoline | Xylene | Benzo(h)quinoline-4-carboxaldehyde | 10 | 202 |

* References 99-324 are on pp. 392-386.

NITROGEN-CONTAINING COMPOUNDS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|--|---|---------|-------------|
| HETEROCYCLIC COMPOUNDS— <i>Continued</i> | | | | |
| 2-Methyl-4-hydroxyquinazoline | — | 4-Hydroxy-2-quinazolinecarboxaldehyde | — | 203 |
| 1-Methylisoquinoline | Dioxane | Isoquinolinaldehyde | 42 | 194 |
| 2-Methyl-4-ketoquinazoline | — | 4-Ketodihydroquinazoline-2-carboxaldehyde | — | 204 |
| 6-Methylphenanthridine | $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ | 6-Phenanthridinecarboxaldehyde | 70 | 205 |
| 5-Methylquinoline | None | 5-Quinolinescarboxaldehyde | — | 206 |
| 6-Methylquinoline | None | 6-Quinolinescarboxaldehyde | — | 206 |
| 7-Methylquinoline | None | 7-Quinolinescarboxaldehyde | 91 | 206 |
| 8-Methylquinoline | None | 8-Quinolinescarboxaldehyde | 70 | 206 |
| 2-Methylquinoraline | Xylene | 2-Quinoralinecarboxaldehyde | 24 | 207 |
| 2-Methyl-1,2,3,4-tetrahydroacridine | — | 2-Methyl-4-keto-1,2,3,4-tetrahydroacridine + 2-methylacridine | — | 45 |
| Nicotine | H_2SO_4 | Nicotinic acid | 75 | 208 |
| 8-Nitrolepidine | $\text{C}_2\text{H}_5\text{OH}$ | 8-Nitrocinchoninaldehyde | 53 | 209, 210 |
| Papaverine | $\text{CH}_3\text{CO}_2\text{H}$ | Papaveraldine | — | 211 |
| 1-Phenyl-3-methyl-4,5-diketo-2-pyrazoline | $\text{C}_2\text{H}_5\text{OH}$ | 1,1'-Diphenyl-3,3'-dimethyl-5,5'-dihydroxy-4,4'-bipyrazole | — | 195 |
| 1-Phenyl-3-methylfava-zole | — | No reaction | — | 195 |
| 2-Picoline | $\text{CH}_3\text{CO}_2\text{H}$ | Pyrazole blue | — | 195 |
| | $\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$ | 2-Pyridinecarboxaldehyde | — | 45 |

* References 94-324 are on pp. 332-356.

NITROGEN-CONTAINING COMPOUNDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|----------------------------------|---|---------|-------------|
| <i>HETEROCYCLIC COMPOUNDS—Continued</i> | | | | |
| 2-Picoline (<i>Continued</i>) | Xylene | Picolinic acid + 2-pyridinecarboxaldehyde | — | 46 |
| 3-Picoline | H ₂ SO ₄ | Nicotinic acid | 50 | 46, 208 |
| Quinaldine | Dioxane | 2-Quinolinedicarboxaldehyde | 50 | 46, 94 |
| | Dioxane | Quinaldine | 91 | 212 |
| | Dioxane | 2-Hydroxy-1,2-di-quinolyloethanone (aged SeO ₂) | 84 | 94 |
| | Xylene | 2-Quinolinedicarboxaldehyde | 68 | 213 |
| Quinoline | H ₂ SO ₄ | Nicotinic acid | 75 | 208 |
| 1,2,3,4-Tetrahydroacridine | — | 1,2,3,4-Tetrahydro-4-acridone + acridine | — | 45 |
| 2,3,8-Trimethyl-5-nitroquinoline | C ₂ H ₅ OH | 3,8-Dimethyl-5-nitroquinoline-2-carboxaldehyde | 33 | 47 |
| 2,3,8-Trimethylquinoline | C ₂ H ₅ OH | 3,8-Dimethylquinoline-2-carboxaldehyde | 82 | 47 |

MISCELLANEOUS

| | | | | |
|--------------------|------------------|--------------|---|-----|
| Ethyl diazoacetate | H ₂ O | Not isolated | — | 214 |
| Nitromethane | Dioxane | Formic acid | — | 215 |

PHENOLIC COMPOUNDS

| | | | | |
|------------------------------|---|---------------------------------|---|---------|
| 2-Acetoxy-1-naphthol | C ₂ H ₅ OH | No reaction | — | 164 |
| Anethole | — | p-Methoxycinnamaldehyde | — | 216 |
| 4,4'''-Dihydroxyquaterphenyl | — | No reaction | — | 217 |
| Dimethyldihydroresorcinol | CH ₃ CO ₂ C ₂ H ₅ | Anhydrodimethone selenium oxide | — | 45, 218 |

* References 99-324 are on pp. 382-385

PHENOLIC COMPOUNDS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---------------------|------------------|---|---------|-------------|
| Isoeugenol | — | No reaction | — | 216 |
| Isosafrole | — | Piperonylacrolein + dihydrosafrole + 3-ethoxysafrole + $C_{10}H_{10}O_3$ + $C_{10}H_8O_2Se$ | — | 85 |
| 3-Methyl-1-naphthol | C_2H_5OH | Not isolated | — | 164 |
| 2-Naphthol | $CH_3CO_2C_2H_5$ | <i>bis</i> (Hydroxynaphthyl) selenide | — | 45 |
| Phenol | — | $Se(C_6H_4OH)_2$ | — | 84 |
| Safrole | — | α -Ketodihydrosafrole + β -ketodihydrosafrole + ethoxysafrole + piperonylacrolein | — | 85 |

STERIODS

| | | | | |
|--|------------------------|--|----|----------------|
| $\Delta^{20,22}$ -3 α -Acetoxy-12- β -hydroxynorcholenic acid 23 \rightarrow 12 lactone | $(CH_3CO)_2O$ | $\Delta^{20,22}$ -3 α -Acetoxy-12 β ,21-dihydroxynorcholenic acid 23 \rightarrow 12 lactone | — | 219 |
| Acetylidesacetylpseudo-bufotalin | — | Isolated as dioxime, $C_{12}H_{20}O_5N_2$ | — | 220 |
| Allocholesterol | CH_3CO_2H | Not isolated | — | 23 |
| Δ^5 -Androstene-3- <i>trans</i> -17-diol | CH_3CO_2H | Δ^5 -3,4,7-Androstene-triol | — | 221 |
| Δ^5 -3,17-Androstenediol diacetate | C_6H_6 + CH_3CO_2H | Δ^5 -3,4,7-Androstene-triol | — | 222 |
| Apocholic acid | C_2H_5OH | β -Dihydroxychole-dienic acid | 60 | 23, 223 224 |
| Bromodesoxysarsapogenin | C_6H_6 + CH_3CO_2H | No reaction | — | 225 |
| Bromodigitogenin triacetate | CH_3CO_2H | No reaction | — | 226 |
| 23-Bromodiosgenin acetate | C_6H_6 + CH_3CO_2H | 4-Hydroxybromodiosgenin acetate | — | 227 |

* References 99-324 are on pp. 382-356.

STEROIDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--------------------------------------|---|--|---------|-------------|
| Bromogitogenin di-acetate | CH ₃ CO ₂ H | No reaction | — | 226 |
| Bromosarsapogenin | — | No reaction | — | 105 |
| Bromotigogenin acetate | CH ₃ CO ₂ H | No reaction | — | 228 |
| Calciferol (vitamin D ₂) | C ₂ H ₅ OH | Not isolated | — | 23 |
| 3-O-Carbethoxy-cholesterol | (CH ₃ CO) ₂ O | 3-O-Carbethoxy-4-acetoxycholesterol + 3-O-carbethoxy-6-acetoxy- Δ^4 -3-cholestenol | — | 229 |
| | CH ₃ CO ₂ H | 3-O-Carbethoxy-4-acetoxycholesterol + 3-O-carbethoxy-6-acetoxy- Δ^4 -3-cholestenol + <i>cis</i> - Δ^4 -cholestene-3,4-diol carbonate | — | 229 |
| 3-O-Carbomethoxy-cholesterol | (CH ₃ CO) ₂ O | 3-O-Carbomethoxy-4-acetoxycholesterol + 3-O-carbomethoxy-6-acetoxy- Δ^4 -3-cholestenol | — | 229 |
| | CH ₃ CO ₂ H | 3-O-Carbomethoxy-4-acetoxycholesterol + 3-O-carbomethoxy-6-acetoxy- Δ^4 -3-cholestenol + <i>cis</i> - Δ^4 -cholestene-3,4-diol carbonate | — | 229 |
| Chlorogenin | CH ₃ CO ₂ H | Not isolated | — | 230 |
| Choladienic acid | C ₂ H ₅ OH | Not isolated | — | 23 |
| Cholatrienic acid | C ₂ H ₅ OH | Not isolated | — | 23 |
| 3,6-Cholestanedione | C ₂ H ₅ OH or CH ₃ CO ₂ H | Not isolated | — | 22, 23 |
| α -Cholestanetriol | CH ₃ CO ₂ H | No reaction | — | 23 |
| Cholestanone | C ₂ H ₅ OH or CH ₃ CO ₂ H | 2,3-Cholestanedione | 30 | 22, 23 |
| Cholestene | CH ₃ CO ₂ H | Not isolated | — | 23 |
| $\Delta^{8,14}$ -Cholestene | C ₂ H ₅ OH | $\Delta^{8,14}$ -Cholestadiene | — | 231 |
| Δ^4 -3,5-Cholestenedione | CH ₃ CO ₂ H | Not isolated | — | 22 |
| Cholestenone | CH ₃ CO ₂ H | Not isolated | — | 23 |
| 4-Cholesten-3-one | CH ₃ CO ₂ H | Not isolated | — | 22 |

* References 99-324 are on pp. 382-389.

STEROIDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------------|---|--|----------------|-----------------------|
| Cholesterilene | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Cholesterol | C ₆ H ₆ + CH ₃ CO ₂ H (CH ₃ CO) ₂ O | <i>cis</i> -Δ ^{5,6} -3,4-Cholestenediol <i>cis</i> -Δ ^{5,6} -3,4-Cholestenediol diacetate + Δ ⁴ -3,6-cholestenediol diacetate | 38 25 25 | 97 23, 232, 324 |
| Cholesterol oxide | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Cholesteryl acetate | CH ₃ CO ₂ H | <i>cis</i> -Δ ^{5,6} -3,4-Cholestenediol diacetate + <i>trans</i> -Δ ^{5,6} -cholestenediol diacetate | — | 23, 97 |
| | CH ₃ CO ₂ H | 4-Acetoxy-Δ ⁵ -3-cholestenol + 3-acetoxy-Δ ⁵ -4-cholestenol | 60 5 | 233 |
| | C ₆ H ₆ + CH ₃ CO ₂ H | 3-Acetyl-4-hydroxycholesterol | — | 234 |
| | — | Δ ⁴ -Cholesten-3β,6β-diol | — | 235 |
| Cholesteryl benzoate | CH ₃ CO ₂ H | 3-Benzoyloxy-Δ ⁵ -3,4-cholestenediol + <i>trans</i> -3,4-cholestenediol-3,4-dibenzoate | — | 97 |
| | Dioxane | 3-Benzoyloxy-Δ ⁵ -4-cholestenol | 70 | 233 |
| | — | Δ ⁴ -Cholesten-3β,6β-diol | — | 235 |
| Cholesteryl bromide | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Cholesteryl chloride | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Cholesteryl ether | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Cholesteryl propionate | C ₆ H ₆ + CH ₃ CO ₂ H | 4-Propionyloxy-Δ ⁵ -3-cholestenol | — | 233 |
| Cholic acid | CH ₃ CO ₂ H | No reaction | — | 23 |
| Clinosterol | (CH ₃ CO) ₂ O | Δ ⁴ -3,6-Chlostenediol diacetate | — | 236, 237 |
| Coprostanone | C ₂ H ₅ OH or CH ₃ CO ₂ H | Not isolated | — | 22 |
| Coprosterol | CH ₃ CO ₂ H | Not isolated | — | 23 |

* References 99-324 are on pp. 352-356.

STEROIDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--|---|---|---------|-------------|
| Dehydrodesoxycholic acid | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 23 |
| Dehydroergosterol | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 23 |
| Dehydroergosterol | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Desoxycholic acid | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 23 |
| Desovysarsapogenin | $\text{C}_6\text{H}_6 + \text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 225 |
| α -3(β),7-Dibenzoyl- Δ^4 -cholestene | Dioxane + $\text{CH}_3\text{CO}_2\text{H}$ | α -3(β),7-Dibenzoyl- α - Δ^4 -4(β)-cholestenol | — | 238 |
| Digitaligenin | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 23 |
| Digitoxigenin | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 23 |
| Dihydrochlorogenin | $\text{CH}_3\text{CO}_2\text{H}$ | $\text{C}_{27}\text{H}_{46}\text{O}_6$ | — | 230 |
| Dihydrodesovysarsapogenin | $\text{C}_6\text{H}_6 + \text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 225 |
| Dihydroergosterol | $\text{C}_6\text{H}_6 + \text{C}_2\text{H}_5\text{OH}$ | Dihydroergosterol oxide + ergosterol-D | — | 23 |
| Dihydroergosterol oxide | $(\text{CH}_3\text{CO})_2\text{O}$ $\text{C}_2\text{H}_5\text{OH}$ | Ergosterol-B ₂ acetate | — | 23 |
| Dihydrogitogenin | — | Not isolated | — | 23 |
| α -Dihydrolanosteryl acetate | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 228 |
| Dihydrosarsapogenin | — | γ -Lanosteryl acetate | — | 239 |
| Dihydrostigogenin | — | No reaction | — | 105 |
| Dihydrotycholadienic acid | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 228 |
| 3,12-Diketocholelamic acid | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 23 |
| α -Ergostene | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| α -Ergosterol | $\text{C}_2\text{H}_5\text{OH}$ | Dehydroergosterol | — | 23, 223 |
| β -Ergosterol | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 23 |
| α -Ergostenone | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Ergosterol | $\text{C}_2\text{H}_5\text{OH} + \text{C}_6\text{H}_6$ | Dehydroergosterol | — | 23, 240 |
| Ergosterol-B ₂ | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Ergosterol-D | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Ergosterol peroxide | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Ergosteryl benzoate | $\text{C}_2\text{H}_5\text{OH}$ | Not isolated | — | 23 |
| Gitogenin | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 226 |
| Gitovigenin | $\text{CH}_3\text{CO}_2\text{H}$ | Not isolated | — | 23 |

* References 22-324 are on pp. 352-356

STERIODS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|---|---|---------|-------------|
| 5-Hydroxy-3,6-cholestanedione | CH ₃ CO ₂ H | Not isolated | — | 23 |
| 3-Hydroxy-6-cholestanone | CH ₃ CO ₂ H | Not isolated | — | 22 |
| 3-Hydroxy-6-cholestanone acetate | CH ₃ CO ₂ H | No reaction | — | 23 |
| 12-Ketocholanic acid | CH ₃ CO ₂ H | No reaction | — | 23 |
| Ketohydroxyoestrin | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Lanosteryl acetate | C ₂ H ₅ OH | Monoacetate of diol, C ₃₀ H ₅₀ O ₂ | — | 239 |
| Lumisterol | C ₂ H ₅ OH | Not isolated | — | 23 |
| Methyl β-3-acetoxy-Δ ^{20,22} -norallocholelate | (CH ₃ CO) ₂ O | β-3-Acetoxy-21-hydroxy-Δ ^{20,22} -norallocholelic acid lactone | — | 241 |
| Methyl apocholate | C ₂ H ₅ OH | β-Dihydroxycholelidenic acid (after hydrolysis) | — | 23, 223 |
| Methyl dihydroxycholelate | C ₂ H ₅ OH | β-Dihydroxycholelidenic acid (after hydrolysis) | — | 23, 223 |
| 5-Methyl-Δ ⁵ -3,6-norcholestenediol | C ₂ H ₅ OH | 5-Methyl-Δ ⁵ -3,6,11-norcholestenetriol | 25 | 242 |
| Oxycholestenone | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Oxycholesterilene | CH ₃ CO ₂ H | No reaction | — | 23 |
| Pregnane carbonyl compounds | — | Pregnane polycarbonyl compounds | — | 243 |
| Δ ⁵ -Pregnene-3(β),20(α)-diol diacetate | C ₂ H ₅ ÷ CH ₃ CO ₂ H | Δ ⁵ -3,4,20-Pregnene-triol | — | 222 |
| Δ ⁵ -Pregnene-3,17-diol-21-one | — | Δ ⁵ -3,4,17,20,21-Pentahydroxypregnene ÷ Δ ⁴ -3,6,17,20,21-pentahydroxypregnane | — | 244 |
| Pseudocholestane | CH ₃ CO ₂ H | No reaction | — | 23 |
| Pseudocholestane | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Pseudocholesterol | CH ₃ CO ₂ H | Not isolated | — | 23 |
| Pseudosarsasapogenin | — | Not isolated | — | 245 |
| Sarsasapogenin | — | Not isolated | — | 105 |
| Sitosterol | CH ₃ CO ₂ H | Not isolated | — | 23 |

* References 99-324 are on pp. 232-356.

STEROIDS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|----------------------|---|---------|-------------|
| Sitosteryl acetate | $C_6H_6 + CH_3CO_2H$ | 4-Hydroxysitosterol diacetate + 6-hydroxysitosterol diacetate | — | 246 |
| | — | Δ^5 -3,4-Stigmastenediol + Δ^5 -3,4-sitostenediol + Δ^4 -3,6-sitostenediol | — | 247 |
| Stigmasterol | CH_3CO_2H | Not isolated | — | 23 |
| 1,9,10,11-Tetrahydro-1,2-cyclopentenophenanthrene | C_2H_5OH | 9,10-Dihydro-1,2-cyclopentenophenanthrene | — | 248 |
| Tetrahydrodiosgenin triacetate | $C_6H_6 + CH_3CO_2H$ | Δ^5 -3,4-Dihydroxycholestene (after hydrolysis) | — | 249 |
| Tetrahydrosarsapogenin | — | No reaction | — | 105 |
| Tigogenin | CH_3CO_2H | Not isolated | — | 228 |
| Zymosterol | C_2H_5OH | Not isolated | — | 23 |

SULFUR-CONTAINING COMPOUNDS

| | | | | |
|------------------------|------------|---------------------------|----|----------|
| 3-Acetylthianaphthene | Dioxane | 3-Thianaphthene-glyoxal | 50 | 250 |
| Acetylthiourea | H_2O | Not isolated | — | 251 |
| Allylthiourea | H_2O | Not isolated | — | 251 |
| Benzylthiourea | H_2O | Not isolated | — | 251 |
| Benzyl p-telyl sulfone | — | No reaction | — | 252 |
| Diacetylthiourea | H_2O | Not isolated | — | 251 |
| Diethylbenzylthiourea | H_2O | Not isolated | — | 251 |
| Diethylthiourea | H_2O | Not isolated | — | 251 |
| Dimethylphenylthiourea | H_2O | Not isolated | — | 251 |
| Disulfides | — | Sulfoxides + sulfones | — | 5 |
| Dithiocarbamates | ROH | Selenium dithiocarbamates | — | 253 |
| Ethyl ethanesulfenato | — | No reaction | — | 254 |
| 2-Hydroxythianaphthene | C_2H_5OH | Isothioindigo | — | 255, 256 |

* References 99-324 are on pp. 352-356.

SULFUR-CONTAINING COMPOUNDS—*Continued*

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------------|----------------------------------|---|---------|-------------|
| 3-Hydroxythianaphthene | C ₂ H ₅ OH | Thioindigo | — | 255 |
| 2-Methylbenzothiazole | Xylene | 2-Benzothiazolecarboxaldehyde | 20 | 207 |
| Methylthiourea | H ₂ O | Not isolated | — | 251 |
| Phenylthiourea | H ₂ O | Not isolated | — | 251 |
| Thioacetamide | H ₂ O | Not isolated | — | 251 |
| Thiobenzamide | H ₂ O | Not isolated | — | 251 |
| Thiophenol | — | Diphenyl disulfide + (C ₆ H ₅) ₂ Se | — | 86 |
| Thiourea | H ₂ O | Not isolated | — | 251 |
| Trimethylthiourea | H ₂ O | Not isolated | — | 251 |

TERPENES

| | | | | |
|---|-------------------------------------|--|----|---------|
| Abietic acid | C ₂ H ₅ OH | 6-Hydroxyabietic acid | 26 | 23, 257 |
| | — | Dehydroabietic acid | — | 258 |
| 6-Acetoxyepicamphor | (CH ₃ CO) ₂ O | 6-Acetoxycamphorquinone | 57 | 259 |
| $\Delta^{12,13,18,19}$ -2-Acetoxy-11-ketooleadiene | Dioxane | C ₂₂ H ₄₀ O ₅ | — | 260 |
| $\Delta^{10,11,12,13,18,19}$ -2-Acetoxy-11-ketooleatriene | CH ₃ CO ₂ H | C ₂₂ H ₄₀ O ₅ | — | 260 |
| 2-Acetoxy-5-oxo-camphane | (CH ₃ CO) ₂ O | 2-Acetoxy-5,6-camphanedione | — | 259 |
| β -Amyradienol acetate | Dioxane | β -Amyradienedionol acetate | — | 261 |
| β -Amyradienonyl acetate | CH ₃ CO ₂ H | O ₅ -Acetate | 65 | 262 |
| β -Amyradienonyl benzoate | CH ₃ CO ₂ H | O ₅ -Benzoate | — | 262 |
| β -Amyradienyl acetate | CH ₃ CO ₂ H | β -Amyrenonyl acetate | — | 263 |
| β -Amyranonyl acetate | — | No reaction | — | 264 |
| β -Amyratrienol acetate | CH ₃ CO ₂ H | β -Amyradiendionyl acetate | — | 265 |
| β -Amyrene | CH ₃ CO ₂ H | Dehydro- β -amyrene | — | 266 |
| β -Amyrenonyl acetate | CH ₃ CO ₂ H | O ₇ -Acetate | 68 | 262 |

* References 99-324 are on pp. 332-356.

TERPENES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|--------------------------------|---|---|---------|-------------|
| β -Amyrenonyl benzoate | $\text{CH}_3\text{CO}_2\text{H}$ | O_2 -Benzoate | 60 | 262 |
| β -Amyrin acetate | $\text{CH}_3\text{CO}_2\text{H}$ | Dehydro- β -amyrin acetate | — | 266, 267 |
| | Dioxane | β -Amyradienediolol acetate | 44 | 261 |
| δ -Amyrin acetate | Dioxane | β -Amyradienediolol acetate | — | 261 |
| β -Amyrin benzoate | $\text{CH}_3\text{CO}_2\text{H}$ | Dehydro- β -amyrene benzoate | — | 23, 266 |
| β -Amyranonol acetate | Dioxane | Enol- β -amyrandiolol acetate | — | 268 |
| Arnidenediol diacetate | — | Diacetylarnidenediol | — | 269 |
| 3-Benzylcamphor | None | 3-Benzylidenecamphor | 95 | 26, 27 |
| Betulinal diacetate | $\text{CH}_3\text{CO}_2\text{H}$, (CH_3CO) ₂ O, or C_6H_6 | Diacetoxy lupenal | — | 270 |
| Borneol | None | Camphorquinone | 60 | 24, 271 |
| 3-Bromocamphor | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | 26 |
| | None | Camphorquinone | 55 | 26 |
| Campheno | — | Camphene selenide | — | 272 |
| Camphor | $\text{C}_2\text{H}_5\text{OH}$ | Camphorquinone | 73 | 26, 27 |
| | Toluene | Camphorquinone | 89 | 26, 27 |
| | Xylene | Camphorquinone | 89 | 26, 27 |
| | (CH_3CO) ₂ O | Camphorquinone | 93 | 24, 25, 28 |
| | None | Camphorquinone | 65 | 24 |
| Camphoric mononitrile | Toluene | Camphoric anhydride | 11 | 27 |
| Carvomenthene | $\text{CH}_3\text{CO}_2\text{H}$ | Cymene + carvotanacetone + carvotanacetol acetate | 24 | 273 |
| | | | 28 | |
| | $\text{C}_2\text{H}_5\text{OH}$ | Carvotanacetone | 26 | 50, 60 |
| Caryophyllene | $\text{C}_4\text{H}_9\text{OH}$ | Resin | — | 274 |
| | (CH_3CO) ₂ O | Caryophyllenol acetate | — | 275 |
| Cedrene | (CH_3CO) ₂ O | Cedrenol acetate | 80 | 276, 277 |
| | $\text{C}_4\text{H}_9\text{OH}$ | Cedrenal | — | 276 |
| | | | — | 26 |
| 3-Chlorocamphor | $\text{CH}_3\text{CO}_2\text{H}$ | No reaction | — | |
| | None | Camphorquinone | 32 | 26, 27 |
| | | | — | 278 |
| <i>l</i> - α -Curcumene | $\text{C}_2\text{H}_5\text{OH}$ | No reaction | — | |
| <i>l</i> - β -Curcumene | $\text{C}_2\text{H}_5\text{OH}$ | <i>l</i> - β -Curcumenal | — | 278 |

* References 99-324 are on pp. 352-386.

TERPENES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|------------------------------------|-------------------------------------|--|----------|-------------|
| Cyclocitral | C ₂ H ₅ OH | Safranal | — | 279 |
| Cymene | — | Cumaldehyde | — | 280 |
| Dihydrocaryophyllene | C ₄ H ₉ OH | Dihydrocaryophyllenealdehyde | 36 | 274 |
| Dihydrolycorinone | CH ₃ CO ₂ H | No reaction | — | 281 |
| Dipentene | — | Ketone group at 8-position + cymene + cumaldehyde | — | 50, 280 |
| d-Epicamphor | (CH ₃ CO) ₂ O | 5,6-Diketocamphane | — | 282 |
| l-Epicamphor | (CH ₃ CO) ₂ O | Camphorquinone | 74 | 282 |
| 3-Ethylcamphor | — | Camphorquinone + 3-ethylidenecamphor | 12 | 26, 27 |
| R-Homocamphenilone | — | Carbocamphenilone | — | 283 |
| 3-Hydroxycamphor | C ₂ H ₅ OH | Camphorquinone | 40 | 26, 27 |
| | None | Camphorquinone | 85 | 26, 27 |
| Iso- α -amyrenonol acetate | CH ₃ CO ₂ H | Iso- α -amyradienonol acetate | 50 | 284 |
| Iso- α -amyrenonol benzoate | CH ₃ CO ₂ H | Iso- α -amyradienonol benzoate | — | 284 |
| Iso- β -amyrenonyl acetate | CH ₃ CO ₂ H | Acetate; m.p. 208° | — | 285 |
| Isoborneol | — | Camphorquinone | — | 271 |
| α -Isocamphenilone | (CH ₃ CO) ₂ O | α -Isocamphenilquinone | 66 | 286 |
| Isofenchone | (CH ₃ CO) ₂ O | Isofenchoquinone | — | 28, 29 |
| l-Isofenchone | (CH ₃ CO) ₂ O | Isofenchoquinone | — | 30 |
| Isonitrosocamphor | C ₂ H ₅ OH | α -Camphoric mononitrile + camphoric anhydride | 20 12 | 26 |
| | Toluene | α -Camphoric mononitrile + camphoric anhydride | 36 36 | 26 |
| | None | α -Camphoric mononitrile + camphoric anhydride | 23 27 | 26, 27 |
| Isonoragathenol acetate | C ₆ H ₆ | α,β -Ketone, C ₁₁ H ₁₈ O ₂ (after dehydrogenation) | — | 287 |

* References 29-324 are on pp. 352-356.

TERPENES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|--|---|---------|-------------|
| 2-Keto-1,7-dimethyl-7-norcamphanecarboxylic acid | $\text{CH}_3\text{CO}_2\text{H}$ | α -Oxoisoketopinic acid | — | 288 |
| Leucodrin | — | No reaction | — | 289 |
| d-Limonene | — | Cymene + mixture of terpene alcohols and aldehydes or ketones | — | 290 |
| α -Lupene | $\text{CH}_3\text{CO}_2\text{H}$ or C_6H_6 | Lupenal | 45 | 291, 292 |
| Lupeol | $(\text{CH}_3\text{CO})_2\text{O}$ | Lupenol acetate | — | 269 |
| Lupeol acetate | $(\text{CH}_3\text{CO})_2\text{O}$ | Lupenediol diacetate + ketolupeol acetate | 50 | 293, 294 |
| Lupeol benzoate | C_6H_6 | Ketolupeol acetate | 60 | 293 |
| | $\text{CH}_3\text{CO}_2\text{H}$ | Lupenol acetate | 58 | 292 |
| | C_6H_6 | A ketolupeol benzoate | 53 | 293 |
| | $(\text{CH}_3\text{CO})_2\text{O}$ | Ketolupeol benzoate | 42 | 294 |
| Menthene | $\text{C}_2\text{H}_5\text{OH}$ | Δ^3 -Menthene-5-one | 12 | 50, 60 |
| Menthol | $\text{C}_2\text{H}_5\text{OH}$ | Hydroxythymoquinone + thymol + menthone | — | 271 |
| Menthone | $\text{C}_2\text{H}_5\text{OH}$ | Hydroxythymoquinone | 8 | 295 |
| | $\text{C}_2\text{H}_5\text{OH}$ | Diosphenol | 15 | 4 |
| Methyl $\Delta^{12,13,18,19}$ -2-acetoxy-11-keto-30-oleadienate | Dioxane | $\text{C}_{30}\text{H}_{48}\text{O}_7$ | — | 260 |
| Methyl acetyldehydrooleanolate | $\text{CH}_3\text{CO}_2\text{H}$ | Diketodehydro ester, $\text{C}_{30}\text{H}_{48}\text{O}_6$, + methyl oleanolate | — | 296 |
| Methyl acetyldeoxyglycyrrhetate | $\text{CH}_3\text{CO}_2\text{H}$ | Methyl acetyldehydrodeoxyglycyrrhetate | — | 297 |
| Methyl acetyloleanolate | $\text{CH}_3\text{CO}_2\text{H}$ | Methyl acetyldehydrooleanolate | — | 298 |
| Methyl acetylsumaresinate | $\text{CH}_3\text{CO}_2\text{H}$ | Methyl acetyldehydrosumaresinate | — | 298 |
| Methyl ketoacetyloleanolate | $\text{CH}_3\text{CO}_2\text{H}$ | Acetate, $\text{C}_{30}\text{H}_{48}\text{O}_7$ | — | 262 |

* References 99-324 are on pp. 352-386.

TERPENES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|--|---|----------|------------------|
| Myrcene | C ₂ H ₅ OH | Myrcenol + myrcenal + myrcenone | — | 49 |
| 4- <i>p</i> -Nitrophenylcamphor | (CH ₃ CO) ₂ O | 4- <i>p</i> -Nitrophenylcamphorquinone | — | 299 |
| Nopinene | H ₂ O | Pinocarvone + pinocarveol | 35 | 34, 300 |
| | C ₂ H ₅ OH | Pinocarveol + carvopinone | 42 | 301 |
| | (CH ₃ CO) ₂ O or CH ₃ CO ₂ H | Pinocarveol + pinocarvyl acetate + carvopinone + pinocarvone | — | 302 |
| | C ₂ H ₅ OH, (CH ₃) ₂ CO, C ₆ H ₆ , C ₆ H ₅ Cl, (C ₂ H ₅) ₂ O, CCl ₄ , C ₆ H ₅ N, H ₂ O, or none | Mixture of carvopinone and pinocarvone | — | 303 |
| | Dioxane | Tricarboxylic acid anhydride, C ₂₀ H ₃₄ O ₅ | — | 304 |
| A-Nordihydrobetulonic acid methyl ester | Dioxane | Methyl tricarboxylic acid anhydride ester, C ₂₀ H ₃₄ O ₅ | 70 | 304 |
| Norfriedalone | CH ₃ CO ₂ H | Norfriedelenone | — | 305 |
| Norfriedelenone | Dioxane | Norfriedelenedione | — | 305 |
| α-Phellandrene | C ₂ H ₅ OH | Cumaldehyde + cymene | — | 60, 61 |
| Pinene | — | Myrtanol + myrtanol + nopinene + pinadiene | — | 306, 307 |
| | C ₂ H ₅ OH | Myrtanal + myrtanol | 11 35 | 272, 308, 309 |
| | C ₂ H ₅ OH | Verbenone | 35 | 34, 310 |
| | None | C ₁₅ H ₂₄ O | — | 50, 311 |
| Pinocarveol | C ₂ H ₅ OH | Carvopinone | 25 | 302 |
| Piperitone | C ₂ H ₅ OH | Thymol + hydroxythymoquinone | 78 | 60, 61 |

* References 60-324 are on pp. 382-384.

TERPENES—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|-----------------------------------|-------------------------|---|---------|-------------|
| Pulegone | C_2H_5OH | 1-Methyl-4-isopropylidene-2,3-cyclohexanedione + 1-methyl-4-isopropylidene-2,3,5-cyclohexanetrione + 1-methyl-4-isopropylidene-2-ethoxy-5-(or 6)-cyclohexen-3-one + 1-methyl-4-isopropylidene-6-ethoxy-5-(or 6)-cyclohexene-2,3-dione | — | 54 |
| Santenone | CH_3CO_2H | Santenonequinone | 100 | 312, 313 |
| α -Terpineol | — | Hydroxycarvone | — | 314 |
| Tetrahydrobyrnone-carboxylic acid | C_4H_9N | Tetrahydrobyrnone-carboxylic acid | — | 315 |
| Verbanone | C_2H_5OH | Verbenone | — | 316 |
| Yobyrone | Xylene or $(CH_3CO)_2O$ | Yobyrone | — | 315 |

MISCELLANEOUS

| | | | | |
|--------------------------------|---------------|--|---|-----|
| Acetylegonol | CH_3CO_2H | bis-2-(Acetyl- Δ^1 -egonolyl)selenide + bis-2-(acetylegonolyl) selenide | — | 317 |
| | $(CH_3CO)_2O$ | Noregonolonidin acetate + α -bis(acetylegonolyl) selenide + β -bis(acetylegonolyl) selenide | — | 318 |
| 3,4-Benzoxanthone | — | 3,4-Benzoxanthone | — | 319 |
| Castor oil | H_2O | Rubbery substance | — | 320 |
| Cottonseed oil | — | Conjugated unsaturated oils | — | 67 |
| Crotonaldehyde dimethyl acetal | CH_3OH | β -Methoxy- α -keto-butyraldehyde | — | 67 |

* References 99-324 are on pp. 352-355.

MISCELLANEOUS—Continued

| Compound Treated | Solvent | Product | Yield % | Reference * |
|---|-----------------------------------|--|---------|-------------|
| Dibutylmercury | None | $(C_4H_9Hg)_2SeO_3$ | — | 9 |
| Diethylmercury | None | $(C_2H_5)_2Se +$ $(C_2H_5Hg)_2SeO_3$ | — | 9 |
| Diisoamylmercury | None | $(iso-C_5H_{11}Hg)_2SeO_3$ | — | 9 |
| Dipropylmercury | None | $(C_3H_7Hg)_2SeO_3$ | — | 9 |
| Glucose | H ₂ O | Not isolated | — | 321 |
| Linseed oil | — | Conjugated unsaturated oils | — | 67 |
| Lorchel | H ₂ SO ₄ | Not isolated | — | 322 |
| Rubber | — | Product resembling vulcanized rubber | — | 69 |
| Sucrose | H ₂ O | Not isolated | — | 214 |
| Tetrahydroösaletin trimethyl ether | CH ₃ CO ₂ H | Tetrahydroösaletinone trimethyl ether | 25 | 323 |
| Tetrahydropomiferitin tetramethyl ether | CH ₃ CO ₂ H | Tetrahydropomiferitinone tetramethyl ether | 20 | 323 |
| Triphenylarsine | C ₆ H ₆ | Triphenylarsine oxide ÷ triphenylarsine selenide | — | 9 |
| Triphenylphosphine | C ₆ H ₆ | Triphenylphosphine oxide ÷ triphenylphosphine selenide | — | 9 |
| Triphenylstibine | C ₆ H ₆ | Triphenylstibine oxide ÷ triphenylstibine selenide | — | 9 |

* References 99-324 are on pp. 382-386.

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CHAPTER 9

THE HOESCH SYNTHESIS

PAUL E. SPOERRI and ADRIEN S. DuBois *

Polytechnic Institute of Brooklyn

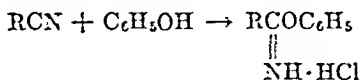
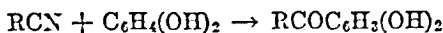
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* Present address, Fuld Bros., Inc.

INTRODUCTION

The Hoesch synthesis * consists in the condensation of a nitrile with a phenol, a polyhydric phenol, or a phenolic ether to form a hydroxyaryl or alkoxyaryl ketone.³ Usually, equimolar quantities of the reactants are dissolved in dry ether, preferably in the presence of a catalyst such as zinc chloride (or ferric chloride), and dry hydrogen chloride is introduced. When phenols are used, imino ether hydrochlorides are sometimes formed as by-products and occasionally represent the only product of the reaction.



This synthesis, which is an extension of the Gattermann aldehyde reaction,^{5,6} is closely related to several well-known procedures leading to ketones, such as the Fries⁷ and the Nencki⁸ reactions.

The Hoesch synthesis has proved to be the most convenient synthetic method for certain polyhydroxyacylophenones and polyhydroxybenzophenones. In these classes, there are twenty-five natural products which have been prepared by this procedure. Among these hydroxy ketones are anthelmintics, antidiarrhetics, and antiseptics. The Hoesch reaction with phloroglucinol has been proposed as a method of converting nitriles to solid derivatives.⁹

Certain substituted nitriles do not undergo the Hoesch reaction because of the influence of one or more additional functional groups.

* A polemical discussion has appeared between Hoesch¹ and Houben² concerning the priority of the discovery of the reaction between alkyl or aryl nitriles and phenols. Since Hoesch was the first to publish a description of this condensation² and since, in articles by Houben⁴ prior to the appearance of the paper by Hoesch, no mention is made that this type of reaction was either carried out or contemplated, the name "Hoesch reaction" is accepted in this chapter. Houben's claim to priority rests on the basis^{2a} that he had suggested privately the possibility of this reaction before the appearance of the early work of Hoesch.

¹ Hoesch, *Ber.*, 60, 359, 2537 (1927).

² Houben, (a) *Ber.*, 59, 2880 (1926); (b) *Ber.*, 60, 1554 (1927); (c) *Ber.*, 61, 1597 (1928).

³ Hoesch, (a) *Ber.*, 48, 1122 (1915); (b) Hoesch and von Zarzecki, *Ber.*, 50, 462 (1917).

⁴ Houben and Schmidt, *Ber.*, 46, 2447, 3616 (1913).

⁵ Gattermann, *Ber.*, 31, 1149, 1765 (1898).

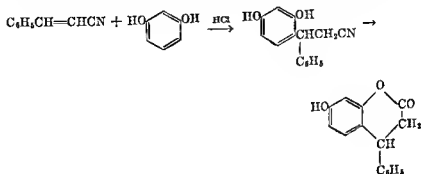
⁶ Calloway, *Chem. Revs.*, 17, 327 (1935).

⁷ Blatt, *Organic Reactions*, I, 342, John Wiley & Sons, 1942.

⁸ Nencki and Sieber, *J. prakt. Chem.*, 23, 147 (1881).

⁹ Howells and Little, *J. Am. Chem. Soc.*, 54, 2451 (1932); Shriner and Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley & Sons, p. 204, 1948.

When an α,β -unsaturated nitrile and a phenol react under the conditions used for the Hoesch synthesis, the phenol adds to the olefinic double bond with formation of a saturated nitrile which hydrolyzes and cyclizes to a dihydrocoumarin.¹⁰ Such reactions have been referred to as "abnormal" Hoesch reactions, although the nitrile group is not involved

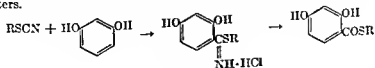


in the initial condensation. Nitriles, other than the α,β -unsaturated nitriles, which yield "abnormal" products appear to be limited almost exclusively to those with a reactive functional group beta to the nitrile group, such as β -halo, β -hydroxy, β -carbethoxy, β -benzoyloxy, β -aldehyde, β -keto, and β -ketimino nitriles. γ -Chlorobutyronitrile also gives an "abnormal" product. The products obtained in the "abnormal" reactions are usually β -arylpropionic acids or β -arylpropionitriles, coumarins, or dihydrocoumarins.

The normal Hoesch synthesis is also applicable to the formation of pyrrol ketones from nitriles and certain pyrroles.



A further extension of the Hoesch synthesis is found in the condensation of thiocyanates with phenols or polyhydric phenols to yield thio esters.

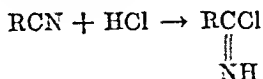


¹⁰ Fischer and Nouri, *Ber.*, **50**, 693 (1917).

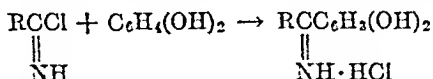
MECHANISM

Hoesch assumed that the reaction involved three separate steps:

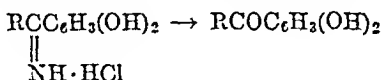
(a) Formation of imino chlorides;



(b) Interaction of imino chlorides with phenol to give ketimine hydrochlorides;

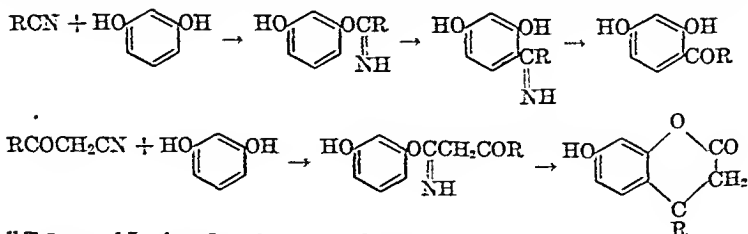


(c) Hydrolysis of the ketimine hydrochlorides to ketones.



In substantiation of this view, Tröger and Luning¹¹ isolated the imino chloride from chloroacetonitrile and hydrogen chloride, and Stephen¹² condensed this addition product with resorcinol to form chlororesacetophenone. Several investigators have isolated and identified the intermediate ketimine hydrochlorides from a variety of Hoesch reactions.^{2a, 13, 14, 15}

Stephen suggested a different mechanism.¹² He postulated that the imino chloride reacted initially with a phenolic hydrogen rather than with a nuclear hydrogen, thus forming an imino ether which might then (1) rearrange to a ketimine hydrochloride ("normal" Hoesch reaction), or (2) if properly constituted condense internally to a coumarin or dihydrocoumarin ("abnormal" Hoesch reaction). This mechanism is untenable,^{2a, 16} since imino ether hydrochlorides cannot be rearranged



¹¹ Tröger and Luning, *J. prakt. Chem.*, [2] 69, 347 (1904).

¹² Stephen, *J. Chem. Soc.*, 117, 1529 (1920).

¹³ Houben and Fischer, *J. prakt. Chem.*, [2] 123, 89 (1929).

¹⁴ Korczynski and Nowakowsky, *Bull. soc. chim. France*, [4] 43, 329 (1928).

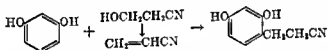
¹⁵ Sonn, (a) *Ber.*, 50, 1292 (1917); (b) *Ber.*, 51, 821 (1918).

¹⁶ Chapman, *J. Chem. Soc.*, 121, 1676 (1922).

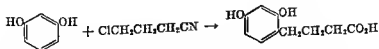
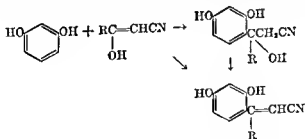
to ketimine hydrochlorides under the influence of heat with or without a catalyst. Moreover, the fact that phenol ethers undergo the Hoesch reaction with the same ease as phenols^{1,17-20} offers additional evidence against an intermediate imino ether.

The "abnormal" Hoesch reaction appears to be merely addition of the phenol to the olefinic double bond of the α,β -unsaturated nitrile.^{10,21,22} The extraordinary susceptibility to addition of the olefin linkage in such nitriles makes this seem likely. The other nitriles which have been reported as undergoing "abnormal" reactions may be divided into three groups: (1) β -hydroxy, β -carbethoxy, β -benzoyloxy, and β -halo; (2) β -aldehydo, β -keto, β -ketimino; (3) γ -halo nitriles.

The mechanism of the initial reaction involved in the first group may be the direct elimination of water, ethanol, hydrogen chloride, etc., between the functional group in the nitrile and a nuclear hydrogen of the phenol, or the substituted nitrile may be converted *in situ* to an α,β -unsaturated nitrile to which the phenol then adds. In the second group, enolization will result in the formation of an α,β -unsaturated



nitrile to which the phenol may add or which may lose water or ammonia by direct reaction with a nuclear hydrogen of the phenol. The members of the third group, the γ -halo nitriles, appear to condense directly with the phenol rather than through an unsaturated intermediate.



¹⁷ Houben and Fischer, *Ber.*, **60**, 1759 (1927).

¹⁸ Shinoda, *J. Pharm. Soc. Japan*, No. 543, 834 (1927) [*C.A.*, **22**, 763 (1928)].

¹⁹ Slater and Stephen, *J. Chem. Soc.*, 117, 309 (1920).

²⁰ Sonn, (a) *Ber.*, **51**, 1829 (1918). (b) *Ber.*, **52**, 923 (1919).

²¹ Langley and Adams, *J. Am. Chem. Soc.*, **44**, 2320 (1922).

²² Marsh and Stephen, *J. Chem. Soc.*, 117, 1633 (1925).

SCOPE AND LIMITATIONS

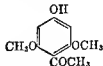
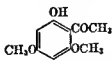
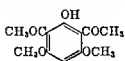
Variations in the Phenols, Phenolic Ethers, and Nitriles

A wide variety of nitriles has been condensed with a relatively restricted number of phenols.^{2a} Phenol and substituted monohydric phenols sometimes react with nitriles to give as products imino ether hydrochlorides, many times to the exclusion of any ketone. Phenol and β -naphthol with acetonitrile, chloroacetonitrile, dichloroacetonitrile, phenylacetonitrile, and benzonitrile give 42 to 74% yields of imino ethers.^{2a} Phenetole with chloro- or bromo-acetonitrile gives very low yields (8%) of ketones.¹⁷ On the other hand, trichloroacetonitrile reacts smoothly with anisole, phenetole, *o*-cresyl ethyl ether, *m*-cresyl ethyl ether, phenyl ether, and veratrole to give ketones, usually in yields varying from 50 to 100%. α -Naphthol reacts with acetonitrile to yield both imino ether and ketone (38%); the yields of ketones from α -naphthol and chloroacetonitrile (55-83%), trichloroacetonitrile (50%), phenylacetonitrile (40%), and benzonitrile (18%) indicate the wide variation that may be expected in this reaction, dependent upon the structure of the nitrile. Similarly, α -naphthyl ethyl ether reacts to give ketones with acetonitrile (2-5%), chloroacetonitrile (86%), and trichloroacetonitrile (95%); anthranyl methyl ether with acetonitrile and benzonitrile also results in formation of ketones. An excess of nitrile with mono- and poly-hydric phenols and their ethers tends to increase the yield of ketones.¹⁷

Extensive investigations on the condensation of nitriles with resorcinol, phloroglucinol, and their ethers indicate that this reaction is very satisfactory for forming polyhydroxy ketones. The yields of ketones from phloroglucinol or its ethers with aliphatic nitriles except those of very complex character are over 70%; resorcinol or its ethers usually give lower yields. Aromatic nitriles do not react so readily as aliphatic nitriles. In only one instance has the introduction of two ketone groups been noted: acetonitrile and phloroglucinol dimethyl ether yield a mix-

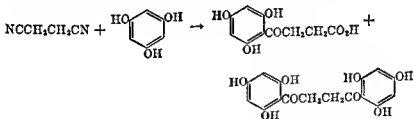
^{2a} Reactions have been described in which an aromatic hydrocarbon or a heterocyclic compound replaces the phenol or phenolic ether. Although these reactions are, strictly speaking, beyond the scope of this chapter, the synthesis of pyrryl ketones is described on p. 397; and the reader's attention is called to the fact that trichloroacetonitrile in the presence of aluminum chloride and hydrogen chloride reacts with benzene, toluene, *o*-, *m*-, and *p*-xylene, mesitylene, naphthalene, and thiophene to yield ω -trichloroacetophenone (70%), ω -trichloro-*p*-methylacetophenone (93%), ω -trichloro-3,4-dimethylacetophenone (69%), ω -trichloro-2,4-dimethylacetophenone (94%), ω -trichloro-2,5-dimethylacetophenone (83%), trichloroacetimidomesitylene (73%), a mixture of ω -trichloroacetophenones (29%), and α -trichloroacetylthiophene (35%). See Houben and Fischer, *J. prakt. Chem.*, [2] 123, 313 (1929).

ture of 1-hydroxy-3,5-dimethoxy-2,6-diacetobenzene and 2-hydroxy-4,6-dimethoxyacetophenone or, possibly, 4-hydroxy-2,6-dimethoxyacetophenone.¹⁸



Of the other polyhydric phenols that have been investigated, orcinol reacts readily to give the corresponding ketones with acetonitrile (63%), benzonitrile (66%), and β -phenylpropionitrile, but not with succinonitrile. 1,2,4-Trihydroxybenzene condenses with *p*-chlorobenzonitrile to give a 55% yield of ketone; pyrogallol, with the same nitrile, gives a 25% yield of ketone, but with benzonitrile or succinonitrile it does not react. The Hoesch reaction is reported not to take place with catechol or hydroquinone.^{14, 22, 24, 25}

Aliphatic dinitriles react with resorcinol and phloroglucinol less readily than mononitriles and usually give mono ketonic acids by the condensation of one nitrile group and hydrolysis of the other. From phloroglucinol and malononitrile or glutaronitrile, a small yield of diketone is reported.^{25a, 26} Apparently dinitriles have not been successfully condensed with any phenols other than those mentioned. In dinitriles



with one aromatic nitrile group and one aliphatic, only the aliphatic group appears to react.²⁷

Cyanogen, which may be considered a dinitrile, reacts with resorcinol to give a mixture of the tetrahydroxybenzil and the dihydroxyphenyl-

¹⁸ Dalal and Nargund, *J. Univ. Bombay*, **7**, Pt. 3, 189 (1938) [*C.A.*, **33**, 3778 (1939)].

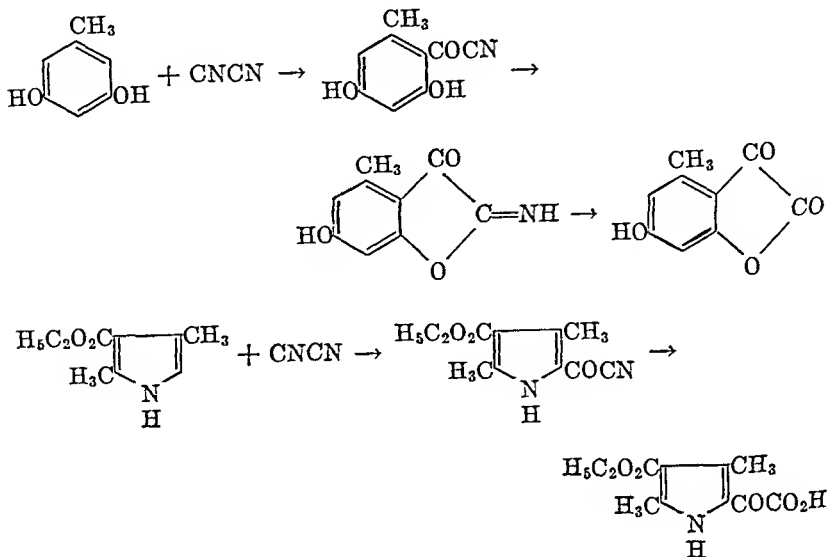
¹⁹ Badhwar, Baker, Menon, and Venkataraman, *J. Chem. Soc.*, 1931, 1541.

²⁰ Bresson and Culbertson, *Proc. Iowa Acad. Sci.*, **36**, 266 (1929) [*C.A.*, **25**, 1230 (1931)].

²¹ Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, **24**, 192 (1935) [*C.A.*, **29**, 7310 (1935)].

²² Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, **22**, 167 (1933) [*C.A.*, **27**, 3927 (1933)].

glyoxylic acid; with orcinol and 2,4-dimethyl-3-carbethoxypyrrole only the glyoxylic acids or derivatives are reported.



By reaction with ethyl cyanocarbonate instead of cyanogen, 2,5-dimethyl-3-carbethoxypyrrole is converted to the ester of the same glyoxylic acid. From 2,4-dimethyl-3-acetylpyrrole, the 5-glyoxylic ester is formed. The yields are excellent (75-97%).

The reactivity of aromatic nitriles is affected adversely by certain *ortho* substituents; *o*-cyano-,^{27,23} *o*-nitro-,^{29,20} *o*-chloro-,³¹ and *o*-methylbenzonitrile³¹ do not react either with resorcinol or phloroglucinol. Even in benzyl cyanide, which contains an aliphatic nitrile group, certain *ortho* substituents cause a reduction in the yield of ketone and sometimes prevent the reaction.²³ *o*-Cyano-^{27,23} and *o*-chloro-benzyl cyanide³¹ react with phloroglucinol, but the *o*-nitro derivative does not. However, halogen, alkyl, hydroxyl, alkoxyl, and nitro substituents in the *meta* and *para* positions of benzonitrile or benzyl cyanide do not interfere with the reaction.

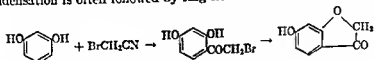
²³ Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, 18, 615 (1929) [*C.A.*, 24, 2443 (1930)].

²⁹ Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, 18, 129 (1929) [*C.A.*, 24, 98 (1930)].

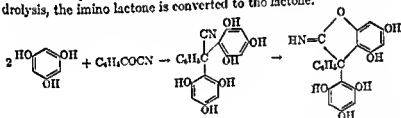
²⁰ Yamashita, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, 24, 205 (1935) [*C.A.*, 29, 7316 (1935)].

³¹ Orito, *Sci. Repts. Tohoku Imp. Univ.*, 1st series, 18, 121 (1929) [*C.A.*, 24, 98 (1930)].

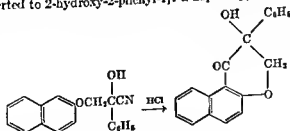
If a nitrile contains an α -halogen or α -hydroxy substituent, the initial condensation is often followed by ring closure to a coumarone.^{19, 20, 22, 23, 24}



The nitriles of α -keto acids, RCOCN , react (a) with one molecule of a phenol to form the normal condensation product, a 1,2-diketone,²² or (b) with two molecules of a phenol to give more complex substances. Thus, acetyl cyanide and propionyl cyanide condense with resorcinol or phloroglucinol to give the expected diketones.²³ Aroyl cyanides, on the other hand, were first reported to undergo a similar reaction,²² but further investigation indicated that the condensation takes place between one mole of the benzoyl cyanide and two of the phenol to give imino lactones.²⁴ The keto group of the aroyl cyanide condenses with two molecules of the phenol followed subsequently by cyclization. Upon hydrolysis, the imino lactone is converted to the lactone.



A few attempts to carry out intramolecular Hoesch reactions have met with very limited success;²⁵ α -2-naphthoxymethylmandelonitrile was converted to 2-hydroxy-2-phenyl-1,4- α -naphthopyranone.²³



²² Karrer and Ferli, *Helv. Chim. Acta*, **4**, 203 (1921).

²³ Klarmann, *J. Am. Chem. Soc.*, **48**, 2358 (1926).

²⁴ Sonn, *Ber.*, **50**, 1262 (1917).

²⁵ Borsche and Diacont, *Ber.*, **63**, 2740 (1930).

²⁶ (a) Borsche and Walter, *Ber.*, **59**, 461 (1926); (b) Borsche, Walter, and Niemann, *Ber.*, **62**, 1360 (1929).

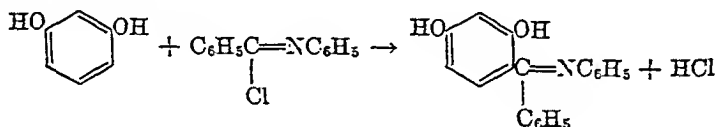
²⁷ Stevens, *J. Chem. Soc.*, 1927, 178.

²⁸ Badhwar and Venkataraman, *J. Chem. Soc.*, 1932, 2420.

In the Hoesch synthesis involving phenol ethers a single isomer is usually obtained. With certain ethers, however, two isomers have been isolated; thus iredol (4-methoxyphloroglucinol) and chloroacetonitrile give 4,6-dihydroxy-5-methoxycoumaran-3-one and 4,6-dihydroxy-7-methoxycoumaran-3-one;³³ orcinol monomethyl ether and acetonitrile give 2-hydroxy-6-methoxy-4-methyl- and 2-hydroxy-4-methoxy-6-methyl-acetophenone.³² Phloroglucinol dimethyl ether and piperonylonitrile give 2-hydroxy-4,6-dimethoxy-3',4'-methylenedioxybenzophenone and 4-hydroxy-2,6-dimethoxy-3',4'-methylenedioxybenzophenone.¹³ If zinc chloride is used as a catalyst only the latter compound is obtained; if ferric chloride is employed both result.¹²

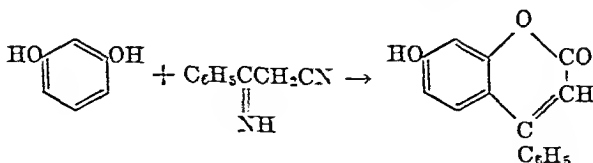
The condensation of aniline and acetonitrile to give *p*-aminoacetophenone is the only reaction reported between an aromatic amine and a nitrile.⁴⁰

Since imino chlorides are intermediates in the initial step of the Hoesch reaction, various imino chlorides may be substituted for the nitriles. Thus benzanilide imino chlorides react with resorcinol to give the Schiff's bases of the ketones which are then hydrolyzed to the corresponding ketones.^{12, 16}



"Abnormal" Hoesch Reactions

The "abnormal" Hoesch reactions run smoothly, but only a few yields have been reported. The reactions of β -aldehydo, β -ketimino, or β -keto nitriles, with resorcinol or phloroglucinol or their alkylated derivatives, fall within the scope of the von Pechmann reaction.^{15b, 41-44} All the com-



³³ Shriner, Matson, and Damschroder, *J. Am. Chem. Soc.*, **61**, 2322 (1939).

³² Hao-Tsing, *J. Am. Chem. Soc.*, **66**, 1421 (1944).

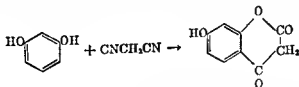
³¹ Baker and Robinson, *J. Chem. Soc.*, **127**, 1981 (1925).

³⁰ Ghosh, *J. Chem. Soc.*, **109**, 105 (1916).

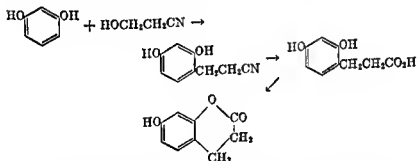
²⁹ von Meyer, *J. prakt. Chem.*, [2] **67**, 342 (1903).

²⁸ von Pechmann and Duisberg, *Ber.*, **16**, 2119 (1883).

pounds represented by the general formulas $\text{RCOCH}(\text{Ar})\text{CN}$, ArCOCH_2CN , $\text{ArC}(\text{=NH})\text{CH}_2\text{CN}$, $\text{ArCOOCH}=\text{C}(\text{Ar})\text{CN}$, and $\text{HCOCH}(\text{Ar})\text{CN}$ give coumarins. An oxocoumarin is obtained from resorcinol and malonitrile or ethyl cyanoacetate in 80% yield. β -Hydroxy-, β -chloro-, and β -carbethoxy-propionitrile react with resorcinol, its monomethyl ether,



orcinol, and phloroglucinol to give in good yields β -arylpropionic acids or the corresponding dihydrocoumarins.^{24, 45}



By the use of excess phenol in the absence of a catalyst, ketones sometimes can be isolated in low yields.⁴⁶ Acrylonitrile and certain cinnamonnitriles are converted smoothly to dihydrocoumarins.^{10, 28} γ -Chlorobutyronitrile and resorcinol form γ -(2,4-dihydroxyphenyl)butyric acid in 21% yield.

Reactions with Pyrroles

In a limited number of reactions pyrroles have been used in the Hoesch synthesis and pyrrol ketones have been formed. Both aliphatic nitriles⁴⁶⁻⁵⁰ and aromatic nitriles⁴⁹ have been employed. Acetonitrile has

⁴⁶ Chapman and Stephen, *J. Chem. Soc.*, 127, 885 (1925).

⁴⁷ Blicke, Faust, Gearien, and Warkynski, *J. Am. Chem. Soc.*, 65, 2465 (1943).

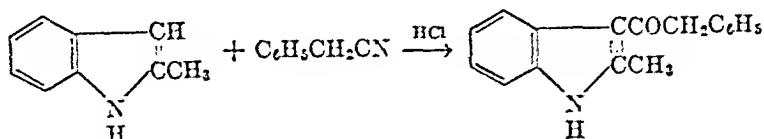
⁴⁸ Fischer, Schneller, and Zerweck, *Ber.*, 55, 2390 (1922).

⁴⁹ Fischer, Weiss, and Schubert, *Ber.*, 55, 1194 (1923).

⁵⁰ Seka, *Ber.*, 56, 2058 (1923).

⁵¹ Kalle and Co., Ger. pat. 365,092 [*Frdl.*, 14, 518 (1926)].

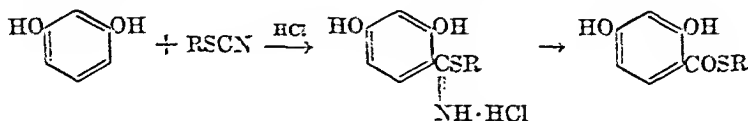
been condensed with 2,4-dimethylpyrrole (54%) and with 2,4-dimethyl-3-carbethoxypyrrole; chloroacetonitrile, with pyrrole (20%), 2,4-dimethylpyrrole, 2,4,5-trimethylpyrrole (57%), 2,5-dimethyl-3-carbethoxypyrrole (75%), and 2-methylindole (20%). 2-Methylindole gives excellent yields with benzyl cyanide, ethyl cyanoacetate, and benzoyl cyanide (70%).⁴⁹ Cyanogen and ethyl cyanocarbonate⁵⁰ have been



condensed in good yields with 2,4-dimethyl-3-carbethoxypyrrole, 2,4-dimethyl-3-acetylpyrrole, and 2,5-dimethyl-3-carbethoxypyrrole.

Reactions with Thiocyanates

Early in the study of the Friedel and Crafts reaction⁵¹ it was demonstrated that phenyl thiocyanate and anisole or related phenol ethers react in the presence of aluminum chloride to give thio esters. It was established much later that this reaction takes place with certain phenols under the experimental conditions of the Hoesch synthesis. Thus, resorcinol or phloroglucinol or orcinol and methyl, ethyl, and *n*-butyl thiocyanates yield the corresponding imino thio ester hydrochlorides which can be hydrolyzed to thio esters.⁵² Phenyl thiocyanate is reported to react with resorcinol, orcinol, and phloroglucinol to give quite stable



imino thio esters which, unlike the corresponding alkyl derivatives, yield acid amides on hydrolysis with hydrochloric acid.^{53,54}

A reaction between phenols and isothiocyanates can occur under the conditions of the Hoesch synthesis. Although this condensation involves neither a nitrile group nor an imino chloride, nevertheless, it is of interest in connection with the condensation of phenols and thiocyanates. Ethyl,

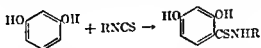
⁵¹ Spath and Fuchs, *Monatsh.*, **42**, 267 (1921).

⁵² Tust and Gattermann, *Ber.*, **25**, 3523 (1892).

⁵³ Kaufmann and Adams, *J. Am. Chem. Soc.*, **45**, 1745 (1923).

⁵⁴ Borsche and Niemann, *Ber.*, **62**, 1743 (1929).

allyl, α -naphthyl, and phenyl isothiocyanates react with α -naphthol, pyrogallol, resorcinol, or phloroglucinol to give amides of thio acids.^{15,16}



SELECTION OF EXPERIMENTAL CONDITIONS

The usual procedure for the Hoesch synthesis is to dissolve equimolar quantities of nitrile and phenol in dry ether and to pass in dry hydrogen chloride to saturation while the reaction mixture is carefully protected from moisture by means of a calcium chloride tube. The temperature has usually been maintained at about 0°. Various procedures are described involving different time factors for completion of the reaction. Sometimes the reaction mixture has been worked up almost immediately after saturation with the hydrogen chloride; sometimes the reaction mixture has been held at 0° from a few hours to a few days.¹⁷ No recommendation with respect to the time necessary is possible though it appears advisable to allow the reaction mixture to stand at least several hours with those nitriles which react slowly with the hydrogen chloride. Hydrogen bromide has been employed in place of hydrogen chloride only in rare instances¹⁸ and probably should be considered only when hydrogen chloride may cause some undesirable side reaction such as the replacement of an active bromine in the nitrile by chlorine.

Dry ether is the solvent that leads to the best yields of product. Glacial acetic acid is a possible substitute for ether and is a better solvent for the imino chlorides;^{19,20} the yields of ketones, however, are usually lower. Other solvents that have been used successfully are chloroform-ether,¹⁴ methyl acetate,¹⁷ and ethyl bromide;¹⁷ those reported as unsuitable are acetic anhydride,¹⁷ dioxane,¹⁷ amyl ether,¹⁴ and benzene.¹⁴

Anhydrous zinc chloride is a desirable though not indispensable catalyst.^{17,19} In general the yields are better if a catalyst is used.¹⁷ Ferric chloride sometimes has advantages over zinc chloride,¹⁷ but comparative experiments have not been sufficiently numerous to make it possible to predict which is to be preferred. Aluminum chloride, a more powerful catalyst, is sometimes necessary.²⁰

¹⁵ Karrer and Weiss, *Helv. Chim. Acta*, **12**, 554 (1929).

¹⁶ Mayer and Mombour, *Ber.*, **62**, 1921 (1929).

¹⁷ Robinson and Venkataraman, (a) *J. Chem. Soc.*, 1926, 2344; (b) 1929, 61.

¹⁸ Freudenberg, Fikentscher, and Harder, *Ann.*, **441**, 157 (1925).

¹⁹ Borsche and Niemann, *Ber.*, **62**, 2043 (1929).

²⁰ Krollpfeiffer, *Ber.*, **56**, 2360 (1923).

When the reaction with hydrogen chloride is complete the hydrolysis and isolation of the ketone may be accomplished in a number of ways. If the ketimine hydrochloride is very insoluble, it may be filtered from the ether and hydrolyzed. Isolation of the ketimine is attended with greater success if a catalyst has not been employed in the reaction. It is reported that the ketimine hydrochlorides may be converted into the less-soluble sulfates by dissolving the hydrochlorides in water and adding dilute sulfuric acid or aqueous ammonium sulfate.^{22, 23}

The reaction mixture containing the ketimine hydrochloride may be treated with water and the ether layer removed. The aqueous solution is then heated, and the ketone which separates is filtered or extracted with a solvent. Sometimes ethanol or aqueous ethanol increases the rate of hydrolysis, but the isolation of pure ketone is often more difficult under these conditions.¹² The hydrolysis may be facilitated by the addition of dilute aqueous ammonia,^{22, 23} sodium hydroxide,²¹ calcium carbonate,²¹ dilute hydrochloric acid,¹² or dilute sulfuric acid.²²

EXPERIMENTAL PROCEDURES

Phloroacetophenone. Detailed directions for the preparation of this ketone from phloroglucinol and acetonitrile in 74-87% yield are given in *Organic Syntheses*.²⁴

4-Hydroxy-1-acetonaphthone and Acetimino- α -naphthyl Ether Hydrochloride.²⁵ Dry hydrogen chloride is bubbled through a solution of 14.4 g. of α -naphthol and 4.1 g. of acetonitrile in absolute ether while the mixture is cooled in an ice bath. After twelve hours the solution takes on a dark-green color and small, green needles of 4-hydroxy-1-acetonaphthone ketimine hydrochloride are deposited in the bottom of the flask. The separation of crystals is complete in three to four days. The supernatant liquid is then decanted from the product, which is crystallized from glacial acetic acid, filtered, washed with ether, and dried. The needles decompose slowly above 200° and finally melt with blackening at 251°. The hydrochloride is stable in the air and is not hygroscopic. The free 4-hydroxy-1-acetonaphthone ketimine, which is insoluble in water, ethanol, and ether, is obtained by treatment with aqueous sodium carbonate.

The ketimine hydrochloride is boiled with water until the white 4-hydroxy-1-acetonaphthone separates from the solution. The crystals

²¹ Bauer and Schoder, *Arch. Pharm.*, 259, 53 (1921).

²² Shoosmith and Haldane, *J. Chem. Soc.*, 125, 113 (1924).

²³ Gulati, Seth, and Venkataraman, *Org. Syntheses, Coll. Vol. 2*, 522 (1943).

are filtered, dried, crystallized from benzene, and washed with petroleum ether; m.p. 198°.

On standing for six to eight weeks, the mother liquors from the crystallization of the ketimine hydrochloride deposit large, pale-green crystals of acetimino- α -naphthyl ether hydrochloride. These are pulverized, dissolved in hot glacial acetic acid, and filtered, and the solution is cooled. The imino ether hydrochloride is precipitated with absolute ether, filtered, washed with ether, and dried; white, very hygroscopic crystals are obtained which decompose above 200°.

β -(2,4-Dihydroxyphenyl)propionic Acid.¹¹ In a 2-l. round-bottomed flask protected with a calcium chloride tube are placed 130 g. of c.p. resorcinol, 90 g. of pure β -chloropropionitrile, and 700 ml. of dry ether. To this solution is added 40 g. of zinc chloride which has been freshly fused and then powdered, dry hydrogen chloride is passed in for five hours, and the flask is allowed to stand for thirty-six hours longer. The mass of crystals that separates is sticky and hard to handle because of the presence of zinc chloride; it is filtered from the red solution and washed with dry ether. The original filtrate is again stoppered and allowed to stand for forty-eight hours, during which time an additional 39 g. of solid separates. After filtering and allowing the filtrate to stand for a week longer, 25 g. more of crystals is obtained.

The total quantity of crystals is dissolved in 450 ml. of water and heated on a steam bath for four hours. An oily layer of β -(2,4-dihydroxyphenyl)propionic acid lactone first separates and solidifies if the heating is interrupted. The layer, however, is not removed, but the reaction mixture is heated further, causing the lactone to go gradually into solution. This solution is cooled and allowed to stand for some hours after which 86.5 g. of β -(2,4-dihydroxyphenyl)propionic acid crystallizes and is filtered. The aqueous filtrate, upon evaporation in vacuum to 175 ml. and cooling, yields a second crop of crystals which weighs 22.5 g. Further concentration and cooling of the filtrate yield only inorganic salts. The total yield of product is thus 109 g. (56%). The substance is almost always light brown, and this color is difficult to remove even after several crystallizations from water with decolorizing carbon. In spite of the color, the product melts sharply at 165° with decomposition, the same temperature as that of the white material obtained by hydrolysis of the pure lactone.

2-Chloroacetylpyrrole.¹² A mixture of 13.6 g. of pyrrole, 20.8 g. of chloroacetonitrile, and 100 ml. of ether is cooled with ice and saturated with hydrogen chloride in such a manner that moisture is excluded.

The precipitated imine hydrochloride is filtered, dissolved in 100 ml. of water, and heated for two hours on a steam bath. The black, solid product is powdered and extracted with carbon tetrachloride in a Soxhlet apparatus; yield 5.7 g. (20%), m.p. 117–119°.

Methyl Thio- β -resorcyate Monohydrate.²² A 1.5-l. wide-mouthed bottle is equipped with a three-holed rubber stopper through which are passed a mechanical stirrer with a mercury seal, an inlet tube with a wide mouth reaching to the bottom of the bottle, and an outlet tube which extends through the stopper and to which is attached a small upright water condenser, the upper end of which is closed with a tube leading through a sulfuric acid wash bottle. In the bottle are placed 110 g. of resorcinol, 73 g. of methyl thiocyanate, 136 g. of anhydrous zinc chloride, and 275 ml. of anhydrous ether. The stirrer is started, and the mixture is agitated for about an hour, until solution is complete. Dry hydrogen chloride is then bubbled into the solution for thirty to forty hours while rapid agitation is maintained constantly. Noticeable warming takes place at the beginning and continues for two to three hours.

After fifteen to twenty-five hours the separation of crystals begins and continues for some time until complete. The mixture is allowed to settle, and the clear mother liquors are decanted. The methyl thio- β -resorcyate imide hydrochloride thus obtained is crystallized twice from hot 15% hydrochloric acid, washed with cold acetone, and then dried at 100–110°. The product is practically pure white and melts at 244–245° (cor.) with decomposition.

The pure imido thio ester hydrochloride is dissolved in three to five times its weight of water, the solution is cooled, and sufficient saturated sodium bicarbonate solution is added to make the mixture alkaline. The methyl thio- β -resorcyate imide which precipitates is filtered and washed with water and then crystallized from methanol; small yellow needles, m.p. 197–199° (cor.) with decomposition.

A solution of 35 g. of once-recrystallized methyl thio- β -resorcyate imide hydrochloride in 1.5 l. of water and 5 ml. of concentrated hydrochloric acid is refluxed for five hours. Upon cooling 25 g. of methyl thio- β -resorcyate monohydrate separates. This is purified by dissolving in a little boiling ethanol to which bone charcoal is added, filtering and reprecipitating with water, and finally recrystallizing from 50% ethanol; colorless needles, m.p. 70–71° (cor.).

TABULAR SURVEY OF THE HOESCH REACTION

In the five tables that follow are listed the imino ethers, ketones, and other products reported in the literature covered by *Chemical Abstracts* through 1947 as having been prepared by the Hoesch and "abnormal" Hoesch reactions.

TABLE I
IMINO ETHER HYDROCHLORIDES *

| Reactants | Products | Yield % | Reference |
|--|--|---------|-----------|
| <i>Phenol</i> | | | |
| CH_3CN | Acetiminophenyl ether hydrochloride | 55 | 2a |
| ClCH_2CN | Chloroacetiminophenyl ether hydrochloride | 73 | 2a |
| Cl_2CHCN | Dichloroacetiminophenyl ether hydrochloride | 70 | 2a |
| Cl_3CCN | Trichloroacetiminophenyl ether hydrochloride | 74 | 2a |
| $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$ | Phenylacetiminophenyl ether hydrochloride | 42 | 2a |
| $\text{C}_6\text{H}_5\text{CN}$ | Benziminophenyl ether hydrochloride | 60 | 2a |
| <i>α-Naphthol</i> | | | |
| CH_3CN | Acetimino- α -naphthyl ether hydrochloride | — | 2a |
| <i>β-Naphthol</i> | | | |
| CH_3CN | Acetimino- β -naphthyl ether hydrochloride | 45 | 2a |
| ClCH_2CN | Chloroacetimino- β -naphthyl ether hydrochloride | 52 | 2a |

* No catalyst was used in the preparation of these imino ether hydrochlorides

TABLE II
 KETONES AND COUMARANONES

| Reactants | Products | Yield % | References * |
|--|---|---------|--------------|
| <i>Anisole</i> Cl_3CCN | 4-Methoxy- ω -trichloroacetophenone | 70 | 17 |
| <i>o-Bromoisole</i> Cl_3CCN | 4-Methoxy-3-bromo- ω -trichloroacetophenone | 5 | 17 |
| <i>Phenole</i> ClCH_2CN | 4-Ethoxy- ω -chloroacetophenone | 8 | 17 |
| BrCH_2CN | 4-Ethoxy- ω -bromoacetophenone | 8 | 17 |
| Cl_3CCN | 4-Ethoxy- ω -trichloroacetophenone | 73-100 | 17 |
| <i>1-Ethoxy-3-methylbenzene</i> Cl_3CCN | 4-Ethoxy-3-methyl- ω -trichloroacetophenone | 79 | 17 |
| <i>1-Ethoxy-3-methylbenzene</i> Cl_3CCN | 4-Ethoxy-2-methyl- ω -trichloroacetophenone | 50-70 | 17 |
| <i>Phenyl ether</i> Cl_3CCN | 4-Phenoxy- ω -trichloroacetophenone | — | 17 |
| <i>1-Naphthol</i> CH_3CN | 4-Hydroxy-1-acetonaphthone | 38 | 2a, 17 |
| ClCH_2CN | 4-Hydroxy-1-chloroacetonaphthone | 55-83 | 2a, 17 |
| Cl_3CCN | 4-Hydroxy-1-trichloroacetonaphthone | 50 | 17 |
| $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$ | 4-Hydroxy-1-phenylacetonaphthone | 40 | 17 |
| $\text{C}_6\text{H}_5\text{CN}$ | 4-Hydroxy-1-benzonaphthone | 18 | 17 |
| <i>1-Ethoxynaphthalene</i> CH_3CN | 4-Ethoxy-1-acetonaphthone | 2-5 | 17 |
| ClCH_2CN | 4-Ethoxy-1-chloroacetonaphthone | 85 | 17 |
| Cl_3CCN | 4-Ethoxy-1-trichloroacetonaphthone | 95 | 17 |
| <i>9-Methoxynaphthalene</i> CH_3CN | 9-Methoxy-10-anthryl methyl ketone | — † | 60 |
| $\text{C}_6\text{H}_5\text{CN}$ | 9-Methoxy-10-anthryl phenyl ketimine hydrochloride | — | 60 |
| <i>Veratrole</i> Cl_3CCN | 3,4-Dimethoxy- ω -trichloroacetophenone | 55 | 17 |
| <i>Resorcinol</i> CH_3CN | 2,4-Dihydroxyacetophenone | 70-84 | 2a, 3a, 19 |
| $n\text{-C}_6\text{H}_{11}\text{CN}$ | n -Amyl 2,4-dihydroxyphenyl ketone | 27 | 64 |
| $\text{CH}_3(\text{CN})_2$ | ω -Cyano-2,4-dihydroxyacetophenone | — | 15a |
| $\text{CN}(\text{CH}_2)_2\text{CN}$ | β -2,4-Dihydroxybenzoylpropionic acid | 21 | 23, 65 |
| $\text{CN}(\text{CH}_2)_3\text{CN}$ | γ -2,4-Dihydroxybenzoylbutyric acid | — | 25 |
| $\text{CN}(\text{CH}_2)_4\text{CN}$ | δ -2,4-Dihydroxybenzoylvaleric acid | — | 25 |
| ClCH_2CN | 2,4-Dihydroxy- ω -chloroacetophenone | 90 ‡ | 12, 20a |
| | 6-Hydroxy-2,3-dihydro-2(1)-benzofuranone | — | 34 |
| BrCH_2CN | 2,4-Dihydroxy- ω -bromoacetophenone | 60-100 | 17, 20b, 66 |
| HOCH_2CN | 2,4-Dihydroxy- ω -hydroxyacetophenone | 38 | 67 |
| | 6-Hydroxy-2(1)-benzofuranone | — | 19 |
| $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -methoxyacetophenone | 70 | 19 |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -ethoxyacetophenone | — | 20b |
| $\text{C}_6\text{H}_5\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -phenoxyacetophenone | — | 20b |
| $\text{C}_6\text{H}_5\text{COOCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -benzoyloxyacetophenone | 80 | 63 |
| $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$ | 2,4-Dihydroxy- ω -phenylacetophenone | 50-75 | 69 |
| $p\text{-ClC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2,4-Dihydroxy- ω - p -chlorophenylacetophenone | — | 63a |
| $m\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{CN}$ | 2,4-Dihydroxy- ω - m -nitrophenylacetophenone | 47 | 23 |
| $p\text{-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CN}$ | 2,4-Dihydroxy- ω - p -methylphenylacetophenone | — | 63a |

* References 64-110 are on p. 412.

† Aluminum chloride as catalyst in benzene as solvent.

‡ No catalyst employed.

TABLE II—Continued

KETONES AND COUMARANONES

| Reactants | Products | Yield % | Refer- ences * |
|--|--|------------|-------------------|
| <i>Benzoinal—Continued</i> | | | |
| $C_6H_5CONHCH_2CN$ | 2,4-Dihydroxy- α -benzoylaminacetophenone | 40 | 66 |
| $C_6H_5OCONHCH_2CN$ | 2,4-Dihydroxy- α -carbethoxyaminacetophenone | 51 | 66 |
| $C_6H_5O_2COCH_2CN$ | 2,4-Dihydroxy- α -carbethoxyoxymacetophenone | — | 66 |
| C_6H_5CN | 2,4-Dihydroxypropiophenone | 31 | 70 |
| $CH_3CHOHCN$ | 6-Hydroxy-3-methyl-2(1)-benzofuranone | — † | 19 |
| $C_6H_5CH_2CH_2CN$ | 2,4-Dihydroxy- β -phenylpropiophenone | 50 † | 33, 71 |
| $3,4-(CH_2O)_2C_6H_3CH_2CH_2CN$ | 2,4-Dihydroxy- β -(3,4-dimethoxyphenyl)propiophenone | 22 † | 72 |
| $3,4-(CH_2O)_2C_6H_3CH_2CH_2CN$ | 2,4-Dihydroxy- β -piperoylpropiophenone | 43 † | 72 |
| 6-Bz-3,4- (CH_2O) $_2$ $C_6H_3CH_2CH_2CN$ | 2,4-Dihydroxy- β - β -benzopiperoylpropiophenone | 47 | 73 |
| α - C_6H_5CN | 3,4-Dihydroxybutiophenone | 25 | 70 |
| $(CH_2)_3CHCHOHCN$ | 2,4-Dihydroxy- α -hydroxyacetophenone | 15 | 30 |
| $(CH_2)_3CHCHClCN$ | 2-Isopropyl-4-hydroxy-2,3-dihydro-2(1)-benzofuranone | 20 | 30 |
| $C_{11}H_{11}CN$ | 2,4-Dihydroxy laurophenone | 20 | 70 |
| C_6H_5CN | 2,4-Dihydroxy benzophenone | 30-40 | 3a, 74 |
| α - $CH_3COOC_6H_4CN$ | 3-Hydroxyanthrone | 13 | 75 |
| m - ClC_6H_4CN | 2,4-Dihydroxy-3'-chlorobenzophenone | 32 | 31 |
| p - ClC_6H_4CN | 2,4-Dihydroxy-4'-chlorobenzophenone | 39 | 31 |
| $2,4-(CH_3COO)_2C_6H_2CN$ | 2,4,2',4'-Tetrahydroxy benzophenone | — | 76 |
| $4-HO_2CH_2OC_6H_2CN$ | 2,4,4',4'-Trihydroxy-3'-methoxybenzophenone | 20 | 86 |
| $3,4-(CH_2O)_2C_6H_2CN$ | 2,4-Dihydroxy-3',4'-methylenedioxy benzophenone | 37 † | 13 |
| $2-CH_3OC_6H_4CHOHCN$ | 2,4-Dihydroxy-2'-methoxybenzoin | — | 76 |
| $C_6H_5COCl=NC_6H_5$ | 2,4-Dihydroxybenzophenone | 20 † | 12, 13 |
| $4-C_6H_5O_2COC_6H_4COCl=NC_6H_5$ | 2,4,4'-Trihydroxybenzophenone | — † | 13 |
| $CNCN$ | 2,4,4',4'-Tetrahydroxybenzoin and 2,4-dihydroxyphenylglyoxylic acid | — † | 32 |
| CH_3COCN | 1-(2,4-Dihydroxyphenyl)propane-1,2-dione | — | 35 |
| C_2H_5COCN | 1-(2,4-Dihydroxyphenyl)butane-1,2-dione | 20 | 35 |
| C_6H_5COCN | 2,4-Dihydroxybenzil | — † | 22 |
| | 2,4,2',4'-Tetrahydroxytriphenyl lactone and lactone | 65 | 26a |
| α - $CH_3OC_6H_4COCN$ | 2,4-Dihydroxy-2'-methoxybenzil | — † | 23 |
| p - $CH_3OC_6H_4COCN$ | 2,4,2',4'-Tetrahydroxy-4'-methoxytriphenyl lactone and lactone | 50-75 | 36a |
| | 2,4-Dihydroxy-4'-methoxybenzil | — | 22 |
| $3,4,5-(CH_2O)_3C_6H_2COCN$ | 2,4-Dihydroxy-3',4',5'-trimethoxybenzil | — † | 22 |
| p - ClC_6H_4COCN | 2,4,2',4'-Tetrahydroxy-4'-chlorotriphenyl lactone and lactone | — † | 36b |
| <i>Benzoinal monomethyl ether</i> CH_3CN | 4-Hydroxy-2-methoxy- and 2-hydroxy-4-methoxyacetophenone | 27 each | 3a |
| $CN(CH_3)_2CN$ | β -2-Hydroxy-4-methoxybenzoylpropionic acid | — | 23 |
| $ClCH_2CN$ | 4-Hydroxy-2-methoxy- and 2-hydroxy-4-methoxy- α -chloroacetophenone | — | 26b |
| $HOCH_2CN$ | 6-Methoxy-2(1)-benzofuranone | — | 19 |
| CH_3OCH_2CN | 2-Hydroxy-4-methoxy- α -methoxyacetophenone | — † | 19 |

* References 64-110 are on p. 412.

† No catalyst employed.

‡ Ferrie chloride as catalyst

§ Aluminum chloride as catalyst in the absence of a solvent.

¶ Chloroform-ether as solvent.

TABLE II—Continued
 KETONES AND COUMARANONES

| Reactants | Products | Yield % | References * |
|--|---|---------|--------------|
| <i>Resorcinol monomethyl ether</i> —Continued | | | |
| CH_3CHOHCN | 6-Methoxy-3-methyl-2(1)-benzofuranone | — | 19 |
| $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2-Methoxy-4-hydroxy- ω -p-methoxyphenylacetophenone and as a by-product 2-hydroxy-4-methoxy- ω -p-methoxyphenylacetophenone | — | 77 |
| | 2-Hydroxy-4-methoxy- ω -p-methoxyphenylacetophenone | — | 78 |
| <i>Resorcinol dimethyl ether</i> | | | |
| CH_3CN | 2,4-Dimethoxyacetophenone | — | 18 |
| ClCH_2CN | 2,4-Dimethoxy- ω -chloroacetophenone | 60 | 20a |
| BrCH_2CN | 2,4-Dimethoxy- ω -bromoacetophenone | — | 68 |
| HOCH_2CN | 2,4-Dimethoxy- ω -hydroxyacetophenone | — † | 19 |
| $\text{C}_2\text{H}_5\text{O}_2\text{COCH}_2\text{CN}$ | 2,4-Dimethoxy- ω -carbethoxyoxyacetophenone | — | 66 |
| Cl_3CCN | 2,4-Dimethoxy- ω -trichloroacetophenone | 100 | 17 |
| <i>6-Hydroxy-3-methylbenzofuran</i> | | | |
| ClCH_2CN | 5-Chloroaceto-3-methyl-6-hydroxybenzofuran | — | 79 |
| $\text{C}_6\text{H}_5\text{CN}$ | 5-Benzoyl-3-methyl-6-hydroxybenzofuran | — | 80 |
| $p\text{-HOC}_6\text{H}_4\text{CN}$ | 5-(4'-Hydroxybenzoyl)-3-methyl-6-hydroxybenzofuran | — | 81 |
| $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CN}$ | 5-(4'-Methoxybenzoyl)-3-methyl-6-hydroxybenzofuran | — | 81 |
| $3,4\text{-(HO)}_2\text{C}_6\text{H}_2\text{CN}$ | 5-(3',4'-Dihydroxy)-3-methyl-6-hydroxybenzofuran | — | 79 |
| <i>6-Hydroxy-3-methyl-2,3-dihydrobenzofuran</i> | | | |
| $\text{C}_6\text{H}_5\text{CN}$ | 3-Methyl-5-benzoyl-6-hydroxy-2,3-dihydrobenzofuran | — | 80 |
| <i>2-Methylresorcinol (2,6-Dihydroxy-1-methylbenzene)</i> | | | |
| CH_3CN | 2,4-Dihydroxy-3-methylacetophenone | — | 82 |
| $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy-3-methyl- ω -methoxyacetophenone | — | 82 |
| <i>Orcinol</i> | | | |
| CH_3CN | 2,4-Dihydroxy-6-methylacetophenone | 63 | 3a |
| $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CN}$ | 2,4-Dihydroxy-6-methyl- β -phenylpropylphenone | — ‡ | 71 |
| $\text{C}_6\text{H}_5\text{CN}$ | 4,6-Dihydroxy-2-methylbenzophenone | 66 | 8a |
| CNCH_3 | 6-Hydroxy-4-methyl-3-keto-2,3-dihydro-2(1)-benzofuranone | — ‡ | 32 |
| <i>Orcinol monomethyl ether</i> | | | |
| CH_3CN | 2-Hydroxy-4-methoxy-6-methyl- and 4-hydroxy-2-methoxy-6-methylacetophenone | 27, 32 | 3a |
| <i>Pyrocatalol</i> | | | |
| $\omega\text{-CH}_3\text{COOC}_6\text{H}_4\text{CN}$ | 2,3,4,2'-Tetrahydroxybenzophenone | 18 | 75 |
| $p\text{-ClC}_6\text{H}_4\text{CN}$ | 2,3,4-Trihydroxy-4'-chlorobenzophenone | 25 | 14 |
| $2,4\text{-(CH}_3\text{COO)}_2\text{C}_6\text{H}_2\text{CN}$ | 2,3,4,2',4'-Pentahydroxybenzophenone | 18 | 75 |
| <i>1,2,4-Trihydroxybenzene</i> | | | |
| CH_3CN | 2,4,5-Trihydroxyacetophenone | Poor | 83 |
| $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,4,5-Trihydroxy- ω -methoxyacetophenone | 50 | 83 |
| $p\text{-ClC}_6\text{H}_4\text{CN}$ | 2,4,5-Trihydroxy-4'-chlorobenzophenone | 55 | 14 |
| $3,4\text{-(CH}_3\text{COO)}_2\text{C}_6\text{H}_2\text{CN}$ | 2,4,5,3',4'-Pentahydroxybenzophenone | 24 † | 14 |
| <i>Phloroglucinol</i> | | | |
| CH_3CN | 2,4,6-Trihydroxyacetophenone | 74-83 | 3a, 57, 63 |
| $\text{C}_2\text{H}_5\text{CN}$ | 2,4,6-Trihydroxypropylphenone | 73 | 84 |
| $n\text{-C}_3\text{H}_7\text{CN}$ | 2,4,6-Trihydroxybutylphenone | 72 | 84, 85 |
| $is\text{-C}_3\text{H}_7\text{CN}$ | 2,4,6-Trihydroxyisobutylphenone | — | 85 |
| $n\text{-C}_4\text{H}_9\text{CN}$ | 2,4,6-Trihydroxyvalerylphenone | 85 | 84 |

* References 64-110 are on p. 412.

† No catalyst employed.

‡ Chloroform-ether as solvent.

TABLE II—Continued

KETONES AND COUMARONOLS

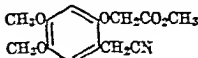
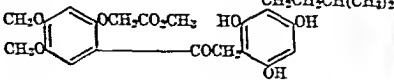
| Reactants | Products | Yield % | References * |
|---|---|---------|--------------|
| <i>Phenylacetal—Continued</i> | | | |
| <i>m</i> -C ₆ H ₄ CN | 2,4,6-Trihydroxyacetophenone | — | 35 |
| <i>m</i> -C ₆ H ₄ CN | 2,4,6-Trihydroxyacetophenone | 27-49 | 69b, 84, 87 |
| <i>iso</i> -C ₆ H ₄ CN | 2,4,6-Trihydroxyacetophenone | 37 | 84 |
| CNCH ₂ CN | <i>iso</i> -(2,4,6-Trihydroxyphenyl)methane and <i>m</i> -cyano-2,4,6-trihydroxyacetophenone | —† | 15a |
| CN(CH ₂) ₂ CN | <i>γ</i> -2,4,6-Trihydroxybenzylstyrene acid and <i>α,γ</i> -di-(2,4,6-trihydroxybenzyl)propane | 15 | 25 |
| CN(CH ₂) ₃ CN | 4,2,4,6-Trihydroxybenzylvaleric acid | — | 25 |
| ClCH ₂ CN | 2,4,6-Trihydroxy- <i>o</i> -chloroacetophenone and 3,5-dihydroxy-2,3-dihydro-2(1 <i>H</i>)-benzofuranone | —† | 34 |
| HOCH ₂ CN | 4,8-Dihydroxy-2(1 <i>H</i>)-benzofuranone | — | 19 |
| CH ₃ COCH ₂ CN | 2,4,6-Trihydroxy-methoxyacetophenone | 75 | 19, 87b |
| CH ₃ CH ₂ CH(CN)CN | 4,6-Dihydroxy-3-ethyl-2,3-dihydro-2(1 <i>H</i>)-benzofuranone | — | 33 |
| C ₆ H ₅ COOCH ₂ CN | 2,4,6-Trihydroxy-benzoyloxyacetophenone | 74‡ | 68 |
| C ₆ H ₅ CH ₂ CN | 2,4,6-Trihydroxy-phenylacetophenone | — | 69a, 87 |
| <i>o</i> -ClC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(2'-chlorophenyl)acetophenone | 20 | 31 |
| <i>p</i> -ClC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(4'-chlorophenyl)acetophenone | — | 69a |
| <i>p</i> -HOC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(4'-hydroxyphenyl)acetophenone | 10-20‡ | 36, 87 |
| <i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(4'-methoxyphenyl)acetophenone | 71, 72 | 89, 90 |
| <i>o</i> -CNC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(2'-cyanophenyl)acetophenone | — | 27 |
| <i>m</i> -CNC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(2'-cyanophenyl)acetophenone | — | 27 |
| <i>p</i> -CNC ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(4'-cyanophenyl)acetophenone | — | 27 |
| <i>o</i> -N ₃ C ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(2'-nitrophenyl)acetophenone | 25 | 28 |
| <i>m</i> -N ₃ C ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(2'-nitrophenyl)acetophenone | 60 | 28 |
| <i>p</i> -N ₃ C ₆ H ₄ CH ₂ CN | 2,4,6-Trihydroxy-(4'-nitrophenyl)acetophenone | 84 | 28 |
| C ₆ H ₅ CH ₂ CH ₂ CN | 2,4,6-Trihydroxy-phenylpropophenone | —‡ | 33, 71 |
| <i>p</i> -HOC ₆ H ₄ CH ₂ CH ₂ CN | 2,4,6-Trihydroxy-(4'-hydroxyphenyl)propophenone | 16‡ | 33 |
| <i>p</i> -CH ₃ COOC ₆ H ₄ CH ₂ CH ₂ CN | 2,4,6-Trihydroxy-(4'-hydroxyphenyl)propophenone | 60 | 31 |
| <i>p</i> -CH ₃ C ₆ H ₄ CH ₂ CH ₂ CN | 2,4,6-Trihydroxy-(4'-methylphenyl)propophenone | — | 62a |
| CH ₃ CH ₂ CH(CN)CN | 4,6-Dihydroxy-3-ethyl-2,3-dihydro-2(1 <i>H</i>)-benzofuranone | — | 33 |
| C ₆ H ₅ CN | 2,4,6-Trihydroxybenzophenone | 63 | 3a, 31, 87 |
| <i>m</i> -ClC ₆ H ₄ CN | 2,4,6-Trihydroxy-3'-chlorobenzophenone | 67 | 31 |
| <i>p</i> -ClC ₆ H ₄ CN | 2,4,6-Trihydroxy-4'-chlorobenzophenone | 43 | 31 |
| <i>o</i> -HOC ₆ H ₄ CN | 1,3-Dihydroxyanthrone | — | 92 |
| | 2,4,6,7-Tetrahydroxybenzophenone | — | 74 |
| <i>m</i> -HOC ₆ H ₄ CN | 2,4,6,7-Tetrahydroxybenzophenone | 27 | 92 |
| <i>p</i> -HOC ₆ H ₄ CN | 2,4,6,7-Tetrahydroxybenzophenone | 15 | 92 |
| 3,4-(HO) ₂ C ₆ H ₂ CN | 2,4,6,7,8-Pentahydroxybenzophenone | 37 | 39 |
| 4-HO-5-CH ₃ OC ₆ H ₃ CN | 2,4,6,7-Tetrahydroxy-3'-methoxybenzophenone | 33 | 36 |
| 5-NO ₂ -3-HOC ₆ H ₃ CN | 1,3-Dihydroxy-7-nitroanthrone | — | 93 |
| 3-(CH ₃ O) ₂ C ₆ H ₃ CN | 2,4,6,7-Tetrahydroxy-3',4'-dimethoxybenzophenone | 46 | 94 |
| CH ₃ COCN | 1-(2,4,6-Trihydroxyphenyl)propano-1,2-dione | 70 | 35 |
| C ₆ H ₅ COCN | 2,4,6-Trihydroxybenzil | —‡ | 23 |
| | 2,4,6,3',4',6'-Hexahydroxytriphenylacetone and isomeric lactone | 90 | 36b |
| <i>o</i> -CH ₃ OC ₆ H ₄ COCN | 2,4,6-Trihydroxy-3'-methoxybenzil | —† | 22 |

* References 64-110 are on p. 412.

† No catalyst employed.

‡ Aluminum chloride as catalyst in the absence of a solvent.

TABLE II—Continued
 KETONES AND COUMARANONES

| Reactants | Products | Yield % | References * |
|---|--|---|--|
| <i>Phloroglucinol—Continued</i> $p\text{-CH}_3\text{OC}_6\text{H}_4\text{COCN}$ | 2,4,6-Trihydroxy-4'-methoxybenzil 2,4,6,2',4',6'-Hexahydroxy-4"-methoxytriphenylacetic acid imino lactone | — 45% — | 22 36b |
| 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ COCN $p\text{-ClC}_6\text{H}_4\text{COCN}$ | 2,4,6-Trihydroxy-3',4',5'-trimethoxybenzil 2,4,6,2',4',6'-Hexahydroxy-4"-chlorotriphenylacetic acid imino lactone | — 45% — 1 | 22 36b |
| <i>Phloroglucinol monomethyl ether</i> $n\text{-C}_6\text{H}_5\text{CN}$ $\text{C}_6\text{H}_5\text{CN}$ $\text{CH}_3\text{OCH}_2\text{CN}$ $\text{C}_6\text{H}_5\text{COOCH}_2\text{CN}$ | 4,6-Dihydroxy-2-methoxybutyrophenone 2,6-Dihydroxy-4-methoxybenzophenone 2,4-Dihydroxy- ω ,6-dimethoxyacetophenone 2,4-Dihydroxy-6-methoxy- ω -benzoyloxyacetophenone | — — 60 7 | 85a 85 95 95 |
| <i>Phloroglucinol dimethyl ether</i> CH_3CN $\text{CH}_3\text{OCH}_2\text{CN}$ $\text{C}_6\text{H}_5\text{COOCH}_2\text{CN}$ $\text{C}_6\text{H}_5\text{CN}$ $p\text{-HOC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2-Hydroxy-4,6-dimethoxyacetophenone and 1-hydroxy-3,5-dimethoxy-2,6-diacetylbenzene ω ,2,4-Trimethoxy-6-hydroxyacetophenone and a small amount of ω ,2,6-trimethoxy-4-hydroxyacetophenone 2,4-Dimethoxy-6-hydroxy- ω -benzoyloxyacetophenone 2- and 4-Hydroxy-2,6-dimethoxybenzophenone 2,4-Dimethoxy-6-hydroxy- ω -(p -hydroxyphenyl)acetophenone and a small amount of 2,6-dimethoxy-4-hydroxy- ω -(p -hydroxyphenyl)acetophenone | — 24 56 — 19 | 18 97 95 98 99 |
| 3,4-(CH ₂ O) ₂ C ₆ H ₂ CN 3,4-(CH ₂ O) ₂ C ₆ H ₂ CN | 2-Hydroxy-4,6-dimethoxy- and 4-hydroxy-2,6-dimethoxy-3',4'-methylenedioxybenzophenone 4-Hydroxy-2,6-dimethoxy-3',4'-methylenedioxybenzophenone | 11% 33 | 13 13 |
| <i>Phloroglucinol trimethyl ether</i> CH_3CN ClCH_2CN BrCH_2CN $p\text{-HOC}_6\text{H}_4\text{CH}_2\text{CN}$ 3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂ CN $\text{C}_6\text{H}_5\text{CHBrCN}$ 3,4-(CH ₃ COO) ₂ C ₆ H ₂ CN 4-HO-3-CH ₃ OC ₆ H ₂ CN 3,4-(CH ₂ O) ₂ C ₆ H ₃ CN | 2,4,6-Trimethoxyacetophenone 2,4,6-Trimethoxy- ω -chloroacetophenone 2,4,6-Trimethoxy- ω -bromoacetophenone 2,4,6-Trimethoxy- ω -(p -hydroxyphenyl)acetophenone 2,4,6-Trimethoxy- ω -(3',4'-dimethoxyphenyl)acetophenone 2,4,6-Trihydroxy- α -bromo- α -phenylacetophenone 2,4,6-Trimethoxy-3',4'-dihydroxybenzophenone 2,4,6,3'-Tetramethoxy-4'-hydroxybenzophenone 2,4,6-Trimethoxy-3',4'-methylenedioxybenzophenone 2,4,6-Trimethoxy-3',4'-methylenedioxybenzophenone | 85 — ‡ — ‡ 10 32 45 16 ** 12 63 § 46 | 13, 18 58 58 99 100, 101 58 13 14 13 13 |
| 1,3,5-Trihydroxy-2-methylbenzene $n\text{-C}_6\text{H}_5\text{CN}$ 1,3,5-Trihydroxy-2-isomethylbenzene | 2,4,6-Trihydroxy-3-methylbutyrophenone | — | 85b |
|  |  | — | 85 |

* References 64-110 are on p. 412.

‡ No catalyst employed.

§ Ferric chloride as catalyst.

¶ Aluminum chloride as catalyst in the absence of a solvent.

‡ Chloroform-ether as solvent.

** Acetic acid as solvent.

TABLE II—Continued
 KETONS AND COUMARONOLS

| Reactants | Products | Yield % | Refer- ences * |
|--|---|------------|-------------------|
| 1,3-Dihydroxy-5-methoxy-2-methyl- benzene $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2,4-Dihydroxy-6-methoxy-3-methyl- ω -(<i>p</i> -hydroxyphenyl)- acetophenone | 44 | 102 |
| 1,3-Dihydroxy-5-methoxy-4-methyl- benzene $m\text{-C}_6\text{H}_4\text{CN}$ | 2,4-Dihydroxy-4-methoxy-3-methylbutyrophenone | — | 103 |
| 1,3-Dimethyl-2,4,6-trihydroxy- benzene $m\text{-C}_6\text{H}_4\text{CN}$ | 2,4,6-Trihydroxy-3,5-dimethylbutyrophenone | — | 85 |
| 1,2,6-Trihydroxy-8-methoxybenzene ClCH_2CN | 4,6-Dihydroxy-5-methoxycoumaran-3-one and 4,6-dihy- droxy-7-methoxycoumaran-3-one | 31, 50 | 39 |
| 1-Hydroxy-3,4,5-trimethoxybenzene ClCH_2CN | 2-Hydroxy-4,5,6-trimethoxy- ω -chloroacetophenone | 42 | 39 |
| $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2-Hydroxy-4,5,6-trimethoxy- ω -(<i>p</i> -methoxyphenyl)- acetophenone | — | 104 |
| 1,3-Dihydroxy-2,5-dimethoxy- benzene CH_3CN | 2,4-Dihydroxy-3,5-dimethoxyacetophenone | — | 105 |
| ClCH_2CN | 2,4-Dihydroxy-3,5-dimethoxy- ω -chloroacetophenone | 25 | 39 |
| $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -3,5-dimethoxyacetophenone | 72 ‡ | 106 |
| 1,3-Dihydroxy-4,5-dimethoxy- benzene $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,6-Dihydroxy- ω -3,4-trimethoxyacetophenone | — ‡ | 106 |
| $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{CN}$ | 2,6-Dihydroxy-3,4-dimethoxy- ω -(<i>p</i> -methoxyphenyl)- acetophenone | 29 | 107 |
| 1,4-Dimethoxy-2,5-dibenzoyl- benzene CH_3CN | 2,4-Dihydroxy-3,6-dimethoxyacetophenone | 75 | 108 |
| $\text{CH}_3\text{OCH}_2\text{CN}$ | 2,4-Dihydroxy- ω -3,6-trihydroxyacetophenone | 62 | 109 |
| | 3-Hydroxy-4-benzoyl- ω -3,6-trimethoxyacetophenone | 31 | 110 |

* References 64–110 are on p. 412.

‡ No catalyst employed.

TABLE III
 PRODUCTS FROM "ABNORMAL" HOESCH REACTION PRODUCTS

| Reactants | Products | Yield % | Reference |
|--|--|---------|-----------|
| <i>2-Naphthol</i> $C_6H_5COOCH=C(C_6H_5)CN$ | 2-Phenyl-3,4- β -naphthopyrone | — | 38 |
| <i>Resorcinol</i> $CH_3COCH(C_6H_5)CN$ | 7-Hydroxy-3-phenyl-4-methylcoumarin | — | 41 |
| $HCOCH(C_6H_5)CN$ | 7-Hydroxy-3-phenylcoumarin | — | 24 |
| $C_6H_5COOCH=C(C_6H_5)CN$ | 7-Hydroxy-3-phenylcoumarin | — | 24 |
| $C_6H_5C(=NH)CH_2CN$ | 7-Hydroxy-4-phenylcoumarin | —† | 155 |
| $C_6H_5CH(CN)COCO_2C_2H_5$ | 3-Phenyl-4-carbethoxy-7-hydroxycoumarin | —‡ | 59 |
| $CNCH_2CO_2C_2H_5$ | 7-Hydroxy-4-oxocoumarin | — | 152, 61 |
| $HOCH_2CH_2CN$ | β -(2,4-Dihydroxyphenyl)propionic acid | — | 21 |
| $ClCH_2CH_2CN$ | β -(2,4-Dihydroxyphenyl)propionic acid | 56‡ | 21 |
| | β -(2,4- and 2,6-Dihydroxyphenyl)propionic acid | 71 | 45 |
| | β -(2,4- and 2,6-Dihydroxyphenyl)propionic acid; 2,4- and 2,6-dihydroxyphenyl β -2,4-dihydroxy- phenethyl ketone | — | 45 |
| $C_6H_5O_2COCH_2CH_2CN$ | Same four products as above | — | 45 |
| $ClCH_2CH_2CH_2CN$ | γ -(2,4-Dihydroxyphenyl)butyric acid | 21 | 21 |
| $C_6H_5CH=CHC(Cl)=NH$ | 7-Hydroxy-4-phenylhydrocoumarin | —† | 12 |
| <i>Resorcinol monomethyl ether</i> $HCOCH(C_6H_5)CN$ | 7-Methoxy-3-phenylcoumarin | — | 24 |
| $ClCH_2CH_2CN$ | β -(2-Hydroxy-4-methoxyphenyl)propionic acid | — | 45 |
| | β -(2-Hydroxy-4-methoxyphenyl)propionic acid and β -(2-hydroxy-4-methoxyphenyl)propionitrile | — | 21 |
| <i>Acetyl resorcinol monomethyl ether</i> $C_6H_5COOCH=C(C_6H_5)CN$ | 7-Methoxy-3-phenylcoumarin | — | 24 |
| <i>Orcinol</i> $C_6H_5COOCH=C(C_6H_5)CN$ | 7-Hydroxy-5-methyl-3-phenylcoumarin | — | 24 |
| $C_6H_5CH(CN)COCO_2C_2H_5$ | 2-Phenyl-4-carbethoxy-7-hydroxycoumarin | —‡ | 59 |
| $ClCH_2CH_2CN$ | 5-Methyl-7-hydroxyhydrocoumarin | 40 | 21 |
| $CH_2=CHCN$ | 5-Methyl-7-hydroxyhydrocoumarin | — | 21 |
| <i>Pyrogallol</i> $C_6H_5COOCH=C(C_6H_5)CN$ | 7,8-Dihydroxy-3-phenylcoumarin | — | 24 |
| <i>Phloroglucinol</i> $HCOCH(C_6H_5)CN$ | 5,7-Dihydroxy-3-phenylcoumarin | — | 24 |
| $C_6H_5C(=NH)CH_2CN$ | 5,7-Dihydroxy-4-phenylcoumarin | —‡ | 155 |
| $p-CH_3OC_6H_4C(=NH)CH_2CN$ | 5,7-Dihydroxy-4-(4'-methoxyphenyl)coumarin | —‡ | 155 |
| $p-CH_3OC_6H_4COCH_2CN$ | 5,7-Dihydroxy-4-(4'-methoxyphenyl)coumarin | —‡ | 20c |
| $2,4-(CH_3O)_2C_6H_3COCH_2CN$ | 5,7-Dihydroxy-4-(2',4'-dimethoxyphenyl)coumarin | —‡ | 20c |
| $3,4-(HO)_2C_6H_3COCH_2CN$ | 5,7-Dihydroxy-4-(3',4'-dihydroxyphenyl)coumarin | —‡ | 20c |
| $C_6H_5CH(CN)COCO_2C_2H_5$ | 3-Phenyl-4-carbethoxy-5,7-dihydroxycoumarin | —‡ | 59 |
| $CH_2=CHCN$ | 5,7-Dihydroxy-4-oxocoumarin | — | 152, 18 |
| $CNCH_2CO_2C_2H_5$ | 5,7-Dihydroxy-4-oxocoumarin ketimine | —† | 152 |
| $ClCH_2CH_2CN$ | 5,7-Dihydroxyhydrocoumarin | 50 | 21 |
| $C_6H_5CH=CHCN$ | 5,7-Dihydroxy-4-phenylhydrocoumarin | 50 | 10 |
| $p-HOC_6H_4CH=CHCN$ | 5,7-Dihydroxy-4-(4'-hydroxyphenyl)hydrocoumarin | 20 | 10 |
| <i>1,2,4-Trisubstituted pyrone</i> $HCOCH(C_6H_5)CN$ | 6,7-Dihydroxy-3-phenylcoumarin | — | 33 |
| <i>Phloroglucinol dimethyl ether</i> $HCOCH(4-CH_3OC_6H_4)CN$ | 5,7-Dimethoxy-2-(4'-methoxyphenyl)coumarin | — | 24 |
| <i>2,4,5-Trimethoxyphenol</i> $HCOCH(3,4,5-(CH_3O)_3C_6H_2)CN$ | 5,6,7-Trimethoxy-3-(3',4',5'-trimethoxyphenyl)coumarin | — | 24 |
| <i>2-Naphthol monomethyl ether</i> (β -naphthol) | 2-Hydroxy-2-phenyl-1,4- β -naphthopyrone | — | 33 |

† No catalyst employed.

‡ Acetic acid as solvent.

§ Excess phenol and no catalyst used.

TABLE IV
PYRRYL KETONES *

| Reactants | Products | Yield % | Reference |
|--|--|---------|-----------|
| <i>Pyrrole</i> CICH_2CN | 2-Chloroacetylpyrrole | 20 | 46 |
| <i>2,4-Dimethylpyrrole</i> CH_3CN | 2,4-Dimethyl-5-acetylpyrrole | 54 | 48 |
| CICH_2CN | 2,4-Dimethyl-5-chloroacetylpyrrole | 95 | 48 |
| <i>2,4,5-Trimethylpyrrole</i> CICH_2CN | 2,4,5-Trimethyl-3-chloroacetylpyrrole | 67 | 47 |
| <i>2,4-Dimethyl-3-carbethoxypyrrrole</i> CH_3CN | 2,4-Dimethyl-3-carbethoxy-5-acetylpyrrole | — | 47, 50 |
| $\text{C}_6\text{H}_5\text{CN}$ | 2,4-Dimethyl-3-carbethoxy-5-benzoylpyrrole | 93 | 50 |
| $\text{CNCO}_2\text{C}_2\text{H}_5$ | Ethyl 2,4-dimethyl-3-carbethoxypyrryl-5-glyoxylate | 75 | 47 |
| CNCN | 2,4-Dimethyl-3-carbethoxypyrryl-5-glyoxylic acid nitrate | — | 47 |
| CNCH_2CN | 2,4-Dimethyl-3-carbethoxy-5-cyanoacetylpyrrole | 70 | 47 |
| <i>2,4-Dimethyl-3-acetylpyrrole</i> $\text{CNCO}_2\text{C}_2\text{H}_5$ | Ethyl 2,4-dimethyl-3-acetylpyrrole-5-glyoxylate | 84 | 47 |
| <i>2,6-Dimethyl-3-carbethoxypyrrrole</i> CICH_2CN | 2,6-Dimethyl-3-carbethoxy-4-chloroacetylpyrrole | 75 | 47 |
| $\text{CNCO}_2\text{C}_2\text{H}_5$ | Ethyl 2,6-dimethyl-3-carbethoxypyrryl-4-glyoxylate | 97 | 47 |
| <i>2-Methylindole</i> CICH_2CN | 2-Methyl-3-chloroacetylindole | — | 50 |
| $\text{CNCH}_2\text{CO}_2\text{C}_2\text{H}_5$ | Ethyl 2-methylindole-3- β -aminoacrylate | 70 | 49 |
| $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$ | 2-Methyl-3-phenylacetylindole | 70 | 49 |
| $\text{C}_6\text{H}_5\text{CN}$ | 2-Methyl-3-benzoylindole | 70 | 50a |

* All the pyrrol ketones were prepared without using a catalyst

TABLE V
IMINO THIO ESTERS

| Reactants | Products | Reference |
|--|---|-----------|
| <i>Resorcinol</i> CH_3SCN | Methyl thio- β -resorcyrate imide hydrochloride | 53 |
| $\text{C}_2\text{H}_5\text{SCN}$ | Ethyl thio- β -resorcyrate imide hydrochloride | 53 |
| $n\text{-C}_4\text{H}_9\text{SCN}$ | Butyl thio- β -resorcyrate imide hydrochloride | 53, 54 |
| $\text{C}_6\text{H}_5\text{SCN}$ | Phenyl thio- β -resorcyrate imide hydrochloride | 54 |
| <i>Orcinol</i> $\text{C}_6\text{H}_5\text{SCN}$ | Methyl 2,4-dihydroxy-6-methylthiobenzoate imide hydrochloride | 54 |
| <i>Phloroglucinol</i> CH_3SCN | Methyl 2,4,6-trihydroxythiobenzoate imide hydrochloride | 53 |
| $\text{C}_6\text{H}_5\text{SCN}$ | Phenyl 2,4,6-trihydroxythiobenzoate imide hydrochloride | 54 |

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CHAPTER 10

THE DARZENS GLYCIDIC ESTER CONDENSATION

MELVIN S. NEWMAN

The Ohio State University

and

BARNEY J. MAGERLEIN

The Upjohn Company

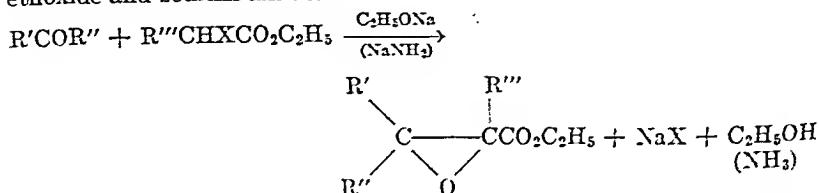
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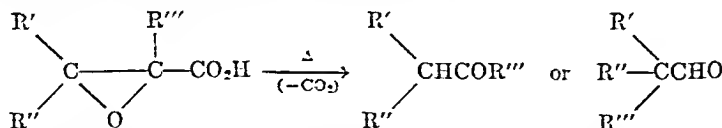
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INTRODUCTION

The Darzens glycidic ester condensation involves the condensation of an aldehyde or ketone with an α -halo ester to produce an α,β -epoxy ester (glycidic ester). The most frequently used condensing agents are sodium ethoxide and sodium amide.



The glycidic esters are of interest primarily because they can be converted into aldehydes and ketones having a higher carbon content than the original aldehydes or ketones. This transformation occurs after hydrolysis to and decarboxylation of the epoxy acids and is accompanied by rearrangement when an aldehyde is formed.



The first synthesis of a glycidic ester was performed by Erlenmeyer,¹ who obtained ethyl β -phenyl- α,β -epoxypropionate by condensing benzaldehyde with ethyl chloroacetate by means of sodium. It remained for Darzens, however, to develop and generalize this reaction.²⁻¹³ He

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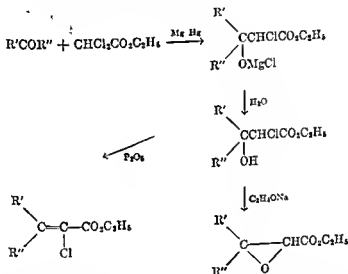
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¹² Darzens and Leroux, *Compt. rend.*, **154**, 1812 (1912).

¹³ Darzens, *Compt. rend.*, **195**, 884 (1932).

preferred sodium ethoxide as the condensing agent. Shortly after the appearance of Darzens' first paper, Claisen¹⁴ reported that sodium amide could be used as the condensing agent. The glycidic ester condensation has not been applied as widely as one would expect in view of the number and variety of compounds that can be prepared by its use.

Darzens^{15, 16, 17} has described another procedure which involves the reaction of aldehydes and ketones with ethyl dichloroacetate and dilute magnesium amalgam. The first product of this reaction is a β -hydroxy α -chloro ester which is quantitatively converted to a glycidic ester by treatment with sodium ethoxide. Alternatively, the hydroxy chloro esters may be dehydrated to yield α -chloro unsaturated esters.



The mechanism of glycidic ester formation probably involves the addition of the enolate of the halo ester to the carbonyl group of the aldehyde or ketone,* followed by an intramolecular nucleophilic dis-

* Early ideas involving addition of the condensing agent to the carbonyl group of the aldehyde or ketone, Fournieu and Billeter, *Bull. soc. chim. France*, [5] 6, 1616 (1939), or the conversion of the aldehyde or ketone to its enolate by the base, Rutowski and Dajew, *Ber.*, 64, 693 (1931), appear inadequate. Scheibler and Tutundzitsch, *Ber.*, 64, 2916 (1931), first suggested the formation of the enolate of the halo ester, but their detailed mechanism appears unnecessarily complicated.

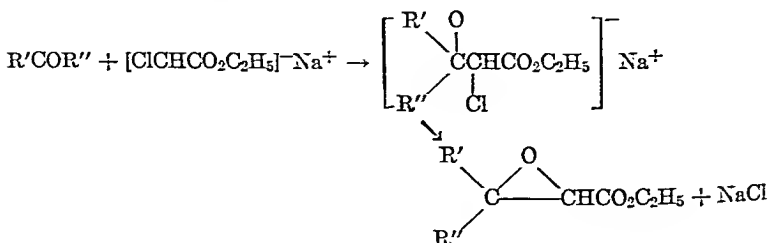
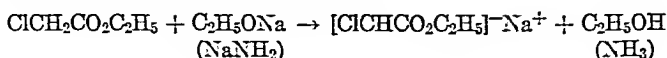
¹⁴ Claisen, *Ber.*, 38, 693 (1905).

¹⁵ Darzens, *Compt. rend.*, 151, 883 (1910).

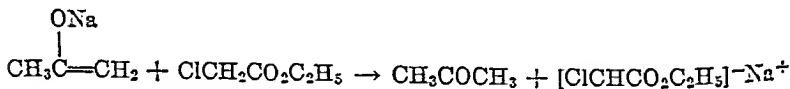
¹⁶ Darzens, *Compt. rend.*, 203, 1374 (1936).

¹⁷ Darzens and Lévy, *Compt. rend.*, 204, 272 (1937).

placement on carbon. The function of the basic condensing agent is to convert the halo ester to its enolate.



Evidence supporting the formation of the enolate of the chloro ester is the fact that about 79% of the theoretical amount of ammonia is evolved on treating a suspension of sodium amide in ether with ethyl chloroacetate.^{18,*} It has been shown that the sodium enolates of ketones react with chloro esters to give glycidic esters.^{18,19} This result is consistent with the above mechanism if it is postulated that the enolate of the ketone reacts with the chloro ester to convert it to its enolate.



SCOPE AND LIMITATIONS

Carbonyl Components

Of the many types of aldehydes and ketones from which the desired condensation products have been isolated, only formaldehyde,⁴ mono-substituted acetaldehydes,⁴ and a few terpene ketones, such as carvone and pulegone,⁴ give generally poor yields. Aromatic aldehydes containing alkyl, alkoxy, methylenedioxy, and chloro groups give fair to good yields. Although no study of the effect of steric hindrance has been made, 2,4,6-trimethylbenzaldehyde is reported to give the expected product,²⁰ but in unstated yield. Aliphatic ketones, including methyl ketones, α,β -unsaturated ketones, and cyclic ketones, react smoothly.

* The hypothesis that a halo ester may form an enolate is supported by the observation that chloromalonic ester may be alkylated to form benzylchloromalonic ester by treatment with sodium ethoxide followed by benzyl chloride, Conrad, *Ann.*, 209, 241 (1881).

¹⁸ Unpublished experiments by Newman and Magerlein at the Ohio State University.

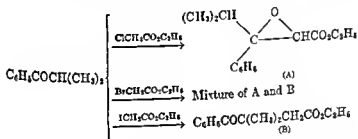
¹⁹ Rutowski and Dajew, *Ber.*, 64, 693 (1931).

²⁰ Chuit and Bolle, *Bull. soc. chim. France*, [4] 35, 200 (1924).

The successful use of a Mannich base, 2-dimethylaminocyclohexanone, has been reported,²¹ but the analogous 4-dimethylamino-2-butanone failed to give the expected ester.²¹ Aromatic and aromatic-aliphatic ketones give very satisfactory yields. The presence of a nuclear chlorine atom appears to improve the yield somewhat.¹³ Although a fairly representative group of aldehydes and ketones has been investigated, no systematic study of the effect of the structure of the carbonyl component on the yield of glycidic ester has been reported.

Halogenated Esters

As a rule, chloro esters are preferable to bromo or iodo esters although bromo esters have been used successfully. With cyclohexanone, it has been shown that the *p*-toluenesulfonate of ethyl glycolate may be substituted for the chloro ester.²² With ethyl chloroacetate, isobutyrophenone yields the glycidic ester, whereas with ethyl iodoacetate it yields an alkylation product, ethyl β,β -dimethyl- β -benzoylpropionate, with ethyl bromoacetate a mixture of the two products results.²³



Very little is known of the condensation of halo esters other than halo acetates, halo propionates, and halo butyrates, ethyl α -chlorolaurate being the only example of a higher ester described.²⁴

The effect of the alkyl group of the halo ester on reactivity or yield has not been investigated to any extent. If sodium amide is the condensing agent, the ethyl ester is preferable to the methyl ester because of increased formation of chloroacetamide with the methyl ester.¹⁴ In experiments involving acetone, benzaldehyde, acetophenone, and cyclohexanone the following alkyl chloroacetates and chloropropionates gave yields comparable to those obtained with methyl and ethyl esters:¹⁵

²¹ Howton, *J. Org. Chem.*, **12**, 379 (1947).

²² Newman and Magerlein, *J. Am. Chem. Soc.*, **63**, 469 (1947).

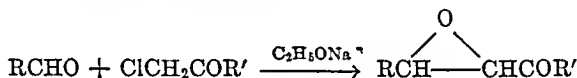
²³ Haller and Ramart-Lucas, *Compt. rend.*, **159**, 143 (1914); Ger. pat. 586,645 [*Fréd.* **20**, 781 (1935)].

propyl and isopropyl, allyl, cyclohexyl, *n*-amyl, benzyl, and 2-ethylhexyl; with β -methallyl and tetrahydrofurfuryl esters the yields were lower. There is some evidence that better yields of condensation products may be obtained with halo amides. An 80% yield of glycidic amide is obtained from acetone and the diethylamide of chloroacetic acid²⁴ whereas with ethyl chloroacetate^{2,14,19} much lower yields result. However, it has not been shown that the glycidic amides can be hydrolyzed and decarboxylated to give aldehydes or ketones in improved yields.

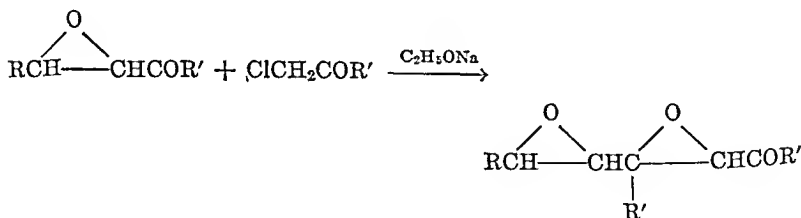
More complex halo esters, such as ethyl β -hydroxy- α -chloropropionate,²⁵ ethyl α,β -dichloropropionate,²⁵ and ethyl α -bromo- β,β -diethoxypropionate,²⁶ have failed to undergo the glycidic ester condensation.

Other Halogenated Compounds

Certain other halogenated compounds have been used in place of halo esters. α -Halo ketones have been condensed with a variety of aldehydes to yield α,β -epoxyketones.²⁷⁻³¹



These epoxyketones may condense with a second molecule of halo ketone to yield $\alpha,\beta,\gamma,\delta$ -diepoxyketones.^{28a}



When 1,4-dibromo-1,4-dibenzoylbutane is treated with sodium cyanide,³² diethylamine,³² sodium acetate,³² or the sodium derivative

²⁴ von Schieckh, *Ber.*, 69, 971 (1936).

²⁵ Yarnall and Wallis, *J. Org. Chem.*, 4, 284 (1939).

²⁶ Oroshnik and Spoerri, *J. Am. Chem. Soc.*, 67, 721 (1945).

²⁷ Widman, (a) *Ann.*, 400, 86 (1913); (b) *Ber.*, 49, 477 (1916).

²⁸ Bodfors, (a) *Ber.*, 49, 2795 (1916); (b) *Ber.*, 51, 192 (1918); (c) *Ber.*, 52, 142 (1919).

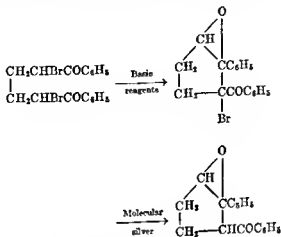
²⁹ Jörlander, (a) *Ber.*, 49, 2782 (1916); (b) *Ber.*, 50, 406, 1457 (1917).

³⁰ Freudenberg and Stoll, *Ann.*, 440, 41 (1924).

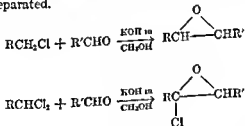
³¹ Murakami and Irie, *Proc. Imp. Acad. (Tokyo)*, 10, 568 (1934) [*C.A.*, 29, 1818 (1935)].

³² Kao and Fuson, *J. Am. Chem. Soc.*, 54, 313 (1932).

of malonic ester ²³ a cyclic epoxyketone is produced; with molecular silver the debrominated analog is obtained.²³



A number of substituted halides of the benzyl ^{24,25,26} and benzal ²⁷ types has been condensed with aldehydes and ketones to give epoxy and α -haloepoxy compounds in yields which, although usually not stated, were often good. Stereoisomeric forms of the epoxy compounds were occasionally separated.



The aldehydes used include benzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, diphenylacetaldehyde, cinnamaldehyde, and furfural; the ketones were fluorenone and 2,7-dibromofluorenone. As halides, *o*- and *p*-nitrobenzyl chloride, 9-chlorofluorene, and 9-bromo-10-anthrone were used.

²³ Kao, *J. Am. Chem. Soc.*, **62**, 356 (1940).

²⁴ (a) Hatsig, Inaugural dissertation, Strasbourg, 1909; (b) Barrow, Inaugural dissertation, Strasbourg, 1909; (c) Chruscinski, Inaugural dissertation, Strasbourg, 1911.

²⁵ Kleucker, *Ber.*, **55**, 1634 (1922).

²⁶ Bergmann and Hervey, *Ber.*, **62**, 902 (1929).

Side Reactions

Few investigators have studied the non-glycidic-ester portion of the reaction products. Some unchanged ketone may usually be recovered. Possible contaminants of the glycidic esters are the isomeric oxygen or carbon alkylation products formed by alkylation of the enolate of the ketone by the halo ester. The boiling ranges reported for the glycidic esters usually cover 5–10°, so that such contamination is entirely possible. The condensation product from β -ionone and ethyl chloroacetate is considered to be a mixture of three isomeric products: glycidic ester; α -keto ester; and the enolic form of the latter.²⁷ Halogen in the condensation products indicates the presence of an α -halogen α,β -unsaturated ester.¹⁴ High-boiling products, including resinous material, are frequently noted. These may result from self-condensation of the aldehyde or ketone²³ or of the halo ester; ethyl chloroacetate in ether reacts with sodium to yield an ethoxy chloro acetoacetate of undetermined structure.²⁹ Vacuum distillation of high-boiling glycidic esters should be done at as low a temperature as possible in order to guard against rearrangement to an α -keto ester.^{42,44,45}

SELECTION OF EXPERIMENTAL CONDITIONS

The reactions are carried out under strictly anhydrous conditions preferably in an inert atmosphere. Often no solvent is used, care being taken to prevent undue temperature rise when the condensing agent is added. It seems best to add the condensing agent to a mixture of the reaction components, of which the halo ester is preferably in some excess.²⁷ It has been found¹⁵ advantageous to use 1.6 moles of chloro ester and 1.6 moles of alkoxide to 1 mole of ketone. During the first stage of the reaction it is well to keep the mixture cold, temperatures as low as -80° being recommended.⁴² However, in a few cases no reaction occurs at -80° , and a temperature of 0° appears to be preferable.¹⁵ After reaction periods ranging from a few hours to a few days, the mixture is usually heated for an hour on a steam bath. The reaction mixture is then treated with dilute acid and the organic products are generally

²⁷ Miles, Lee, Sakai, Wohlsch, MacDonald, Grossi, and Wright, *J. Am. Chem. Soc.*, 70, 1584 (1948).

²³ Weidlich and Daniels, *Ber.*, 72, 1593 (1939).

²⁹ Fittig and Erlenbech, *Ann.*, 259, 15 (1892).

⁴² Troell, *Ber.*, 61, 2498 (1928).

⁴⁴ Kohler, Richtmyer, and Hester, *J. Am. Chem. Soc.*, 53, 211 (1931).

⁴⁵ Pointet, *Compt. rend.*, 148, 417 (1909).

⁴⁶ Yarnall and Wallis, *J. Org. Chem.*, 4, 270 (1933).

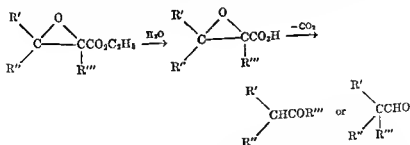
separated by vacuum distillation. At least one glycidic ester rearranged into an α -keto ester at the high temperature needed for vacuum distillation,^{43,44,45} but this rearrangement seems not to be general.

The most frequently used condensing agents are sodium ethoxide and sodium amide. Of these, sodium ethoxide is the reagent of choice in the few reactions where both have been employed.^{23,27,43,44,45} The use of powdered sodium in various solvents seems to be promising.⁴⁶ The sodium ketyl prepared from benzophenone has been used with fair success in one reaction.¹⁹

The effect of solvent on the yields of glycidic esters has not been extensively investigated. Better yields were obtained in the condensation of cyclohexanone with ethyl α -chloropropionate without solvent than with ether, benzene, or benzene-petroleum ether.²⁵ A variety of inert solvents has been used, but the experiments do not permit a conclusion concerning the importance of the solvent. Aromatic hydrocarbons have been recommended as solvents in preparations carried out with the aid of metallic sodium; in the presence of such solvents the sodium chlorido formed in the reaction separates in a colloidal suspension and does not coat the sodium.⁴⁶

CONVERSION OF GLYCIDIC ESTERS INTO ALDEHYDES AND KETONES

Hydrolysis of glycidic esters to and decarboxylation of the resulting glycidic acids usually yield ketones or aldehydes. R' and R'' may



represent hydrogen or alkyl or aryl groups, or may be joined in a ring. If R''' is hydrogen an aldehyde always results; if a methyl group, methyl ketones are formed. The effect of other groups in the R''' position has

⁴³ Linstead and Mann, *J. Chem. Soc.*, 1930, 2070.

⁴⁴ Kayser, *Ann. chim.*, [11] 6, 170 (1936).

⁴⁵ Knorr, Laage, and Weissenborn, Ger. pat. 591,453 [*C.A.*, 23, 2367 (1931)], U. S. pat. 1,899,340 [*C.A.*, 27, 2962 (1933)].

received little attention: when R''' is ethyl, an ethyl ketone is obtained;⁴³ when R''' is *n*-decyl, an aldehyde results.⁴⁴

The conversion of glycidic esters to acids may be effected by the usual alkaline hydrolysis. A special hydrolysis⁴⁴ involves treatment of the ester with one equivalent of sodium ethoxide in absolute ethanol followed by addition of exactly one equivalent of water; addition of dry ether then causes the precipitation of the sodium salt of the glycidic acid.

For the most part, the glycidic acids are converted into the aldehydes or ketones by heating to the decomposition point. Better yields of methyl cyclohexyl ketone may be obtained from α -methyl- α,β -epoxycyclohexylideneacetic acid by two modifications of the above treatment (which gives a 41% yield).⁴⁵ In one, the sodium salt of the glycidic acid is heated with sodium hydroxide at 300° (yield 45–56%); in the other, the glycidic acid is treated with dry hydrogen chloride, and the crude chloro hydroxy acid thus obtained is then heated with semicarbazide hydrochloride in pyridine (yield 75%).

The optimum conditions for pyrolysis of the glycidic acid derived from the condensation of β -ionone and ethyl chloroacetate involve heating in pyridine at 130–135° for one to two hours.⁴⁷ When this same glycidic acid is decarboxylated by heating in the presence or absence of powdered glass or by passage in the vapor phase under reduced pressure over freshly reduced copper on pumice at 140–160°, products having slightly different properties from those of the product obtained by the pyridine method are obtained.⁴⁷ Another group of workers recommends heating in the presence of a small amount of copper powder as the best method for decarboxylating and rearranging this same glycidic acid and the isomeric acid obtained from α -ionone and ethyl chloroacetate,⁴⁸ while a third group of workers reports that no special decarboxylation procedure is necessary for the glycidic ester from β -ionone and ethyl chloroacetate: the glycidic ester is hydrolyzed with cold methanolic sodium hydroxide, the product is extracted in the usual way with ether, and the aldehyde is obtained by vacuum distillation.⁴⁹

A systematic study of the best conditions for the conversion of glycidic esters to aldehydes or ketones is obviously to be desired, and such a study would contribute much to the wider synthetic use of glycidic esters.

⁴³ Monsseron and Granger, *Compt. rend.*, 218, 255 (1944); Monsseron, Winternitz, Granger, Claret, Trinquier, and Combes, *Bull. soc. chim. France*, 1947, 568.

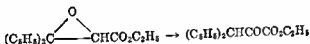
⁴⁴ Heilbron, Johnson, Jones, and Spinks, *J. Chem. Soc.*, 1942, 727.

⁴⁵ Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 30, 1911 (1947).

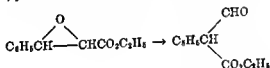
REACTIONS OF GLYCIDIC ESTERS

In addition to their conversion to aldehydes and ketones, discussed in the preceding section, the glycidic esters undergo a number of other reactions which should prove to be valuable in synthetic work. In the paragraphs which follow, examples of these reactions are given. No attempt has been made to list all the examples of any one reaction, but it is believed that all the types of reactions are included.

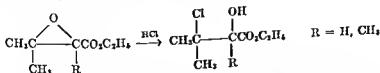
Rearrangement to α - or β -Keto Esters. It has already been pointed out (pp. 420 and 421) that a glycidic ester on heating to a high temperature may undergo rearrangement to a keto ester. Ethyl β,β -diphenylglycidate is isomerized to ethyl β,β -diphenyl- α -ketopropionate on distillation.^{40, 41, 42}



Ethyl β -phenylglycidate, on passage in the vapor state over infusorial earth at 310° , yields the ester of phenylmalonaldehyde acid.⁴³



Reactions with Hydrogen Halides. The addition of hydrogen chloride in dry ether in the cold to ethyl β,β -dimethylglycidate and to ethyl α,β,β -trimethylglycidate results in the formation of α -hydroxy β -chloro esters.* This reaction complements the addition of hypochlorous acid to the corresponding substituted acrylates which yields the isomeric α -chloro β -hydroxy esters.

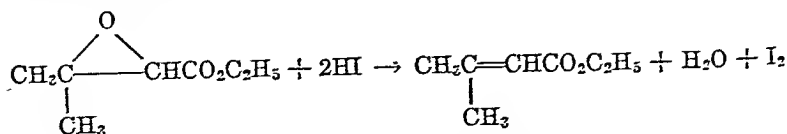


Hydrogen bromide reacts similarly,* but hydrogen iodide yields the acrylate.² This latter reaction constitutes another * method for pre-

* A summary of the methods of preparing $\alpha\beta$ -unsaturated acids by condensation methods is given in the chapter on the Perkin reaction by J. R. Johnson in *Organic Reactions*, Vol. I, p. 233, John Wiley & Sons, New York, 1942.

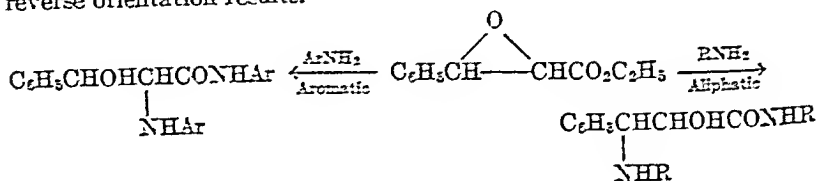
* Tiffeneau and Levy, *Annales soc. chim. argentina*, 16, 144 (1928) [*C.A.*, 24, 2450 (1930)].

paring α,β -unsaturated esters and might be developed into a procedure

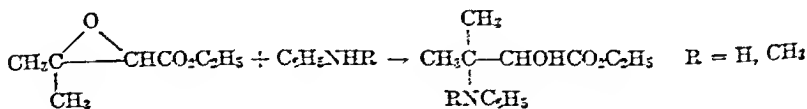


for the quantitative determination of glycidic esters.

Reactions with Ammonia and Amines. Depending upon the reaction conditions, glycidic esters may yield either glycidic amides, hydroxy amino esters, or hydroxy amino amides on treatment with ammonia or amines. The orientation of the hydroxy amino amides appears in doubt. If ammonia or an aliphatic amine is used it is claimed that α -hydroxy β -amino amides are obtained, whereas with an aromatic amine the reverse orientation results.⁴⁹

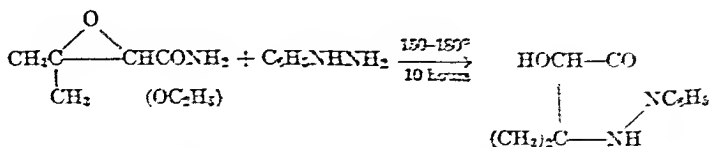


It is stated that with ethyl β,β -dimethylglycidate and aniline or methylaniline an α -anilino- β -hydroxy ester is produced,⁵¹ whereas in a patent the reverse orientation is claimed.⁵⁰



It appears that more work is required before assignment of structure of such amino hydroxy compounds can safely be made by analogy.

With phenylhydrazine, the amide⁵¹ or ethyl ester⁵² of β,β -dimethylglycidic acid yields 1-phenyl-3,3-dimethyl-4-hydroxy-5-pyrazolidone.

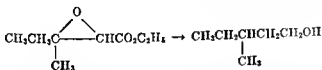


⁴⁹ (a) Fourneau and Billeter, *Bull. soc. chim. France*, [5] 6, 1616 (1939); (b) [5] 7, 593 (1940); (c) Fourneau and Marchal, *Ibid.*, [5] 12, 990 (1945).

⁵⁰ Schickh, Ger. pat. 583,243 [*C.A.*, 28, 260 (1934)].

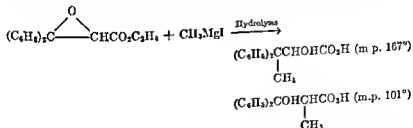
⁵¹ Schickh, Ger. pat. 588,945 [*C.A.*, 28, 1260 (1934)].

Reduction. The reduction of glycidic esters by heating in alcohols with sodium is said to yield mixtures of the saturated acid and of the corresponding primary alcohol. No details of the experimental procedure or yields are reported.⁴² By a similar reduction, β,β -diphenyl-



glycidic ester is reported to yield β,β -diphenyl- α -hydroxypropionic acid.⁴³ However, in view of the previously mentioned rearrangement of this glycidic ester to form a keto ester on vacuum distillation,^{40,41,42} it is possible that the reduction was carried out on the rearranged product.

Grignard Reaction. The product resulting from the action of methylmagnesium iodide on ethyl β,β -diphenylglycidate⁴⁴ followed by hydrolysis is claimed to be β,β -diphenyl- α -hydroxybutyric acid. However, the proof of structure consisted in establishing the non-identity of the reaction product (m.p. 167°) with β,β -diphenyl- β -hydroxy- α -methylpropionic acid (m.p. 101°). The alternative possibility, β,β -diphenyl- α -hydroxy- α -methylpropionic acid, was not ruled out. This latter product would be formed if the glycidic ester rearranged to the α -keto ester.



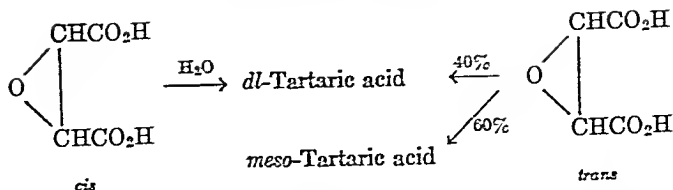
Hydration. Hydration of the *cis* form of ethylene oxide dicarboxylic acid yields *dl*-tartaric acid, whereas the *trans* form yields a mixture of about 40% *dl*-tartaric and 60% *meso*-tartaric acid.⁴⁵

⁴² Verley, *Bull. soc. chim. France*, [4] **35**, 487 (1924).

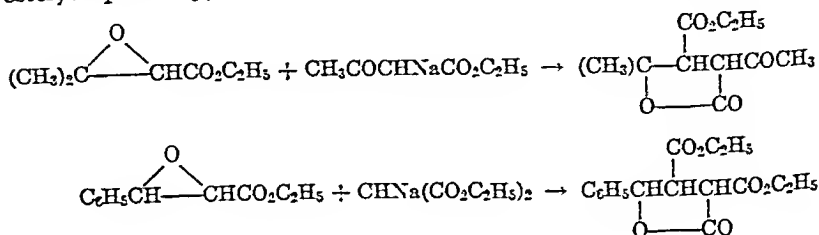
⁴³ Billon-Bardon, *Compt. rend.*, **188**, 1412 (1929).

⁴⁴ Bardon and Ramart, *Compt. rend.*, **183**, 214 (1926).

⁴⁵ Kuhn and Ebel, *Ber.*, **58**, 919 (1925).

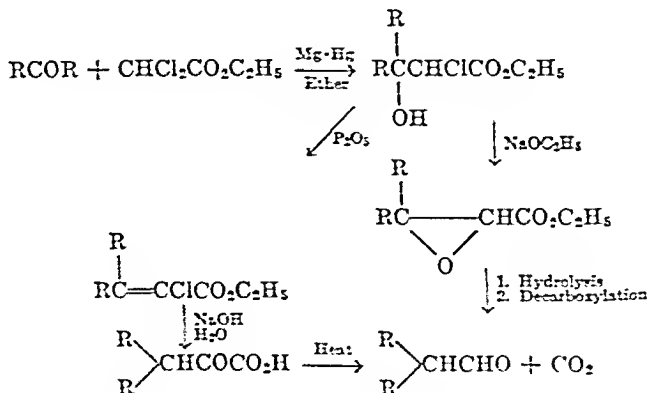


Reaction with Active Methylene Groups. Although details and proof of structure are not given, it is stated that β,β -dimethylglycidic ester and β -phenylglycidic ester react with sodioacetoacetic ester and sodiomalonic ester, respectively, to yield substituted γ -butyrolactones.⁵⁵



THE DICHLOROACETATE SYNTHESIS

Darzens has discovered a series of reactions starting with ethyl dichloroacetate which promises to be of wide applicability. The dichloro ester condenses with aldehydes and ketones in the presence of dilute magnesium amalgam to give excellent yields of α -chloro β -hydroxy esters which can be converted to glycidic esters or to α -chloroacrylic esters.^{15,16,17}



⁵⁵ Chelintsey and Osetrova, *J. Gen. Chem. U.S.S.R.*, 7, 2373 (1937) [*C.A.*, 32, 2092 (1938)].

The α -chloro β -hydroxy esters are formed in almost theoretical yields from ketones. Aliphatic aldehydes, which with α -chloro esters give poor yields of glycidic esters, give yields of 40% to 68% of α -chloro β -hydroxy esters. Ethyl dihydroacetate may replace the dichloro ester, calcium and zinc amalgams the magnesium amalgam, and benzene may replace ether as solvent.¹⁸

The halohydrin esters are quantitatively converted into glycidic esters by treatment with one equivalent of sodium ethoxide. Alternatively, they may be dehydrated to α -chloroacrylates in high yield by phosphorus pentoxide.

The overall conversion of the halohydrin esters to disubstituted acetaldehydes may be effected by two paths as indicated by the above chart. The path involving hydrolysis of the chloroacrylate and decarboxylation of the resulting α -keto acid is recommended by Darzens.¹⁷ The dichloro ester synthesis merits more study and wider use.

EXPERIMENTAL PROCEDURES

Methyl α -Methyl- α,β -epoxycyclohexylideneacetate. (Use of sodium methoxide.)¹⁸ A solution of 49 g. (0.5 mole) of cyclohexanone and 93 g. (0.5 mole) of methyl α -chloropropionate in 200 ml. of anhydrous ether is placed in a flask which has been previously dried by heating with a flame while being swept out with dry nitrogen. The entire reaction is carried out in an atmosphere of dry nitrogen. The reactants are cooled to 5°, and 45.5 g. (0.8 mole) of commercial sodium methoxide (95% pure, The Matheson Company) is added over a period of one hour during which time the reaction mixture is cooled in an ice-water bath and vigorously stirred. The reaction mixture is permitted to warm slowly to room temperature and is stirred for twenty hours, after which the mixture is hydrolyzed by the addition of a cold solution of 30 ml. of concentrated hydrochloric acid in 200 ml. of water. The ether solution is separated and washed successively with two 100-ml. portions of water, 100 ml. of saturated sodium bicarbonate solution, 50 ml. of water, and 100 ml. of saturated sodium chloride solution. After filtration through anhydrous sodium sulfate and distillation of the ether, 78 g. (85%) of methyl α -methyl- α,β -epoxycyclohexylideneacetate is obtained by vacuum distillation, b.p. 116–118°/8.5 mm.

Ethyl α -Methyl- β -*p*-tolylglycidate. (Use of sodium ethoxide, bromo ester, and an aromatic aldehyde.)¹⁷ To a solution of 90 g. (0.5 mole) of ethyl α -bromopropionate and 60 g. (0.5 mole) of *p*-tolualdehyde, cooled in an ice-salt bath, 34 g. (0.5 mole) of freshly prepared sodium ethoxide

¹⁷ Ruzicka and Ehmman, *Helv. Chim. Acta*, **15**, 160 (1932)

up in the usual fashion. Vacuum distillation gives 68 g. (92%) of product, b.p. 166–167°/5 mm.

EXAMPLES OF THE DARZENS GLYCIDIC ESTER CONDENSATION

The literature has been covered through 1947. The compounds are listed according to the increasing carbon content of the empirical formula of the glycidic ester as in the *Chemical Abstracts Formula Index*.

The typical procedure involves slow addition of the condensing agent to a cooled mixture of the carbonyl compound and halo ester with or without a solvent. The condensing agents are:

A. The sodium alkoxide corresponding to the alkyl group of the halo ester.

B. Sodium amide.

C. Sodium, usually powdered.

TABLE I

Glycidic Esters

GLYCIDIC ESTERS

| Carbonyl Component | <div style="text-align: center;"> $\begin{array}{c} \text{R}' \quad \quad \text{O} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{R}'' \quad \quad \text{CO}_2\text{R}''' \end{array}$ </div> | | | | Con- densing Agent | Yield % | Refer- ences * | | | |
|--------------------|---|-------------------|-------------------|---------------------------------|--------------------------|------------|-------------------|--|--|--|
| | Glycidic Ester Formula | | | | | | | | | |
| | R' | R'' | R''' | R'''' | | | | | | |
| Formaldehyde | H | H | CH ₃ — | C ₂ H ₅ — | A | 20-30 | 4 | | | |
| Acetaldehyde | CH ₃ — | H | H | C ₂ H ₅ — | C | — | 19 | | | |
| Acetone | CH ₃ — | CH ₃ — | H | C ₂ H ₅ — | † | 47 † | 19 | | | |
| Acetone | CH ₃ — | CH ₃ — | H | C ₂ H ₅ — | C | 53 | 19 | | | |
| | | | | | A | 60 | 2 | | | |
| | | | | | B | 59 § | 14 | | | |
| Acetaldehyde | CH ₃ — | H | CH ₃ — | C ₂ H ₅ — | A | 20-30 | 4 | | | |
| Propionaldehyde | C ₂ H ₅ — | H | H | C ₂ H ₅ — | A | 20-30 | 4 | | | |
| Acetone | CH ₃ — | CH ₃ — | CH ₃ — | C ₂ H ₅ — | A | — | 3 | | | |
| Butanone | C ₂ H ₅ — | CH ₃ — | H | C ₂ H ₅ — | A | 56 | 44 | | | |
| | | | | | B | 34 | 14, 60 | | | |
| Furfural | C ₄ H ₃ O— | H | H | C ₂ H ₅ — | C | — | 61 | | | |
| | | | | | A | 96(?) | 20 | | | |
| Furfural | C ₄ H ₃ O— | H | CH ₃ — | CH ₃ — | A | 73 | 62 | | | |
| Mesityl oxide | C ₆ H ₇ — | CH ₃ — | H | C ₂ H ₅ — | A | 58 ¶ | 63 | | | |

| | | | | | | | |
|--------------------------|--------------------------|---------|---------|-----------|---|-------|----|
| Cyclopentanone | $-(CH_2)_4-$ | CH_3- | CH_3- | C_3H_7- | A | 41 | 61 |
| Butanone | $iso-C_4H_9-$ | CH_3- | CH_3- | C_3H_7- | A | — | 3 |
| 3-Methyl-2-butanone | C_4H_9- | H | H | C_3H_7- | C | — | 63 |
| 2-Pentanone | $C_5H_{11}-$ | H | H | C_3H_7- | B | 50 | 14 |
| 3-Pentanone | $C_5H_{11}-$ | H | H | C_3H_7- | B | 51 | 14 |
| Benzaldehyde | C_6H_5- | H | H | CH_3- | A | 59 | 19 |
| Furfural | $-(CH_2)_3-$ | H | CH_3- | C_3H_7- | A | 63 | 4 |
| Cyclohexanone | $-(CH_2)_5-$ | H | H | C_3H_7- | A | 85 | 43 |
| Cyclohexanone | $-(CH_2)_5-$ | CH_3- | CH_3- | CH_3- | A | — | 4 |
| Cyclopentanone | $-(CH_2)_4-$ | CH_3- | CH_3- | C_3H_7- | A | 25 | 19 |
| 3-Methylbutanal | $iso-C_4H_9-$ | H | CH_3- | C_3H_7- | A | 20-21 | 43 |
| 2-Pentanone | $C_5H_{11}-$ | CH_3- | CH_3- | C_3H_7- | A | — | 4 |
| o-Chlorobenzaldehyde | $o-C_6H_4Cl-$ | H | H | CH_3- | A | 70 | 3 |
| p-Chlorobenzaldehyde | $p-C_6H_4Cl-$ | H | H | CH_3- | A | 68 | 62 |
| Benzaldehyde | C_6H_5- | H | H | C_3H_7- | C | 55 | 46 |
| Acetophenone | C_6H_5- | H | H | C_3H_7- | A | 25 | 4 |
| 2-Methylcyclohexanone | $-(CH_2)_5CH(CH_3)-$ | H | CH_3- | CH_3- | B | 25 | 14 |
| 3-Methylcyclohexanone †† | $CH_3CH_2CH_2CH_2CH_2-$ | H | CH_3- | C_3H_7- | A | 20 | 21 |
| 3-Methylcyclohexanone | $CH_3CH_2CH_2CH_2CH_2-$ | H | H | C_3H_7- | B | — | 65 |
| 4-Methylcyclohexanone | $-(CH_2)_3CH(CH_3)CH_2-$ | H | CH_3- | C_3H_7- | A | — | 5 |
| 4-Methylcyclohexanone | $-(CH_2)_3CH(CH_3)CH_2-$ | H | CH_3- | C_3H_7- | B | — | 47 |
| 4-Methylcyclohexanone | $-(CH_2)_3CH(CH_3)CH_2-$ | CH_3- | CH_3- | CH_3- | A | — | 5 |
| 4-Methylcyclohexanone | $-(CH_2)_3CH(CH_3)CH_2-$ | CH_3- | CH_3- | CH_3- | A | — | 5 |
| 4-Methylcyclohexanone | $-(CH_2)_3CH(CH_3)CH_2-$ | CH_3- | CH_3- | CH_3- | A | — | 67 |

* References 60-67 are on pp. 439-440.

† Ethyl chloroacetate was added to the mixture instead of the ketone prepared from sodium amide in ether.

‡ The yield was based on the chloro ester.

§ An impure product containing chloro ester and chloro amide.

|| The α -bromo ester was used.

¶ A mixture of methyl and ethyl esters was employed.

** This experiment was run at -85° with no solvent.

†† An optically active ketone was used, and an optically active aldehyde was obtained.

‡‡ The α -bromo ester was used.

TABLE I—Continued

Cyclic Acetals

| Carbonyl Component | Glycidic Ester Formula | | | | Con- densing Agent | Yield % | Refer- ences * |
|--|--|-------------------|------|------|--------------------------|------------|-------------------|
| | R' | R'' | R''' | R''' | | | |
| | | | | | | | |
| Cyclohexanone | —(CH ₂) ₅ — | | | | A | — | 6 |
| 3,3,4-Methoxyoctoxybenzaldehyde (piperonal) | C ₇ H ₅ O ₂ — | H | | | C | — | 68 |
| Benzaldehyde | C ₆ H ₅ — | H | | | A | 50, 71 | 4, 18 |
| p-Tolualdehyde | C ₇ H ₇ — | H | | | C | — | 46 |
| Acetophenone | C ₆ H ₅ — | CH ₃ — | | | A | 60-61 | 2, 58 |
| | | | | | B | —, 64 | 14, 69 |
| | | | | | A | 75 | 62 |
| o-Methoxybenzaldehyde | o-C ₇ H ₇ O— | H | | | A | 82 | 62 |
| m-Methoxybenzaldehyde | m-C ₇ H ₇ O— | H | | | A | — | 46, 68 |
| p-Methoxybenzaldehyde | p-C ₇ H ₇ O— | H | | | C | — | 9 |
| 1-Cyclohexonyl methyl ketone | C ₆ H ₁₁ — | CH ₃ — | | | A | — | 70, 71 |
| 4-Methyl-5-hepten-2-one | C ₆ H ₁₁ — | CH ₃ — | | | A §§ | 45 | 70 |
| | | | | | A | 30 | 72 |
| 6-Methyl-6-hepten-2-one | C ₆ H ₁₁ — | CH ₃ — | | | A | — | — |
| 2-Methylcyclohexanone | —CH(CH ₃)(CH ₂) ₅ — | CH ₃ — | | | A | — | — |

| | | | | | | | |
|--|------------------------|------------------------|---------------|---------------|-------|--------|---------|
| <i>p</i> -Methylacetophenone | C_7H_7- | CH_3- | H | $iso-C_3H_7-$ | A | 47 | 67 |
| Butyrophenone | C_6H_5- | C_4H_7- | H | C_4H_5- | A | 60-63 | 2 |
| <i>p</i> -Ethylacetophenone | C_6H_5- | CH_3- | H | C_4H_5- | A | 60-63 | 2 |
| 4-Phenyl-2-butanone | C_6H_5- | CH_3- | H | C_4H_5- | C | — | 69 |
| <i>p</i> -Methoxybenzaldehyde | $CH_3OC_6H_4-$ | H | $iso-C_3H_7-$ | CH_3- | A ††† | 70 | 62 |
| β -Decalone | $\beta-C_{10}H_{18} <$ | $\beta-C_{10}H_{18} <$ | H | C_2H_5- | A | 90, 71 | 12, 49a |
| 2-Nonanone | $C_7H_{15}-$ | CH_3- | CH_3- | C_4H_5- | A | — | 3 |
| 2-Decanone | $C_8H_{17}-$ | CH_3- | H | C_4H_5- | C | — | 69 |
| 5,6,7,8-Tetrahydro-1-naphthaldehyde | $C_{10}H_{11}-$ | H | H | C_4H_5- | C | — | 46 |
| <i>p</i> -sec-Butylbenzaldehyde | $C_{10}H_{13}-$ | H | H | C_4H_5- | C | — | 40 |
| 2-Methyl-5-isopropylbenzaldehyde | $C_{10}H_{13}-$ | H | H | C_4H_5- | C | — | 20 |
| <i>p</i> -Isopropylbenzaldehyde | $C_6H_{11}-$ | H | CH_3- | C_4H_5- | A | 40 | 70 |
| <i>p</i> -Isopropylacetophenone | $C_6H_{11}-$ | CH_3- | H | C_4H_5- | C | — | 69 |
| β -Decalone | $\beta-C_{10}H_{18} <$ | CH_3- | CH_3- | C_4H_5- | A | — | 12 |
| 2-Undecanone | C_8H_{19} | CH_3- | H | C_4H_5- | A | 60-63 | 2, 75 |
| Benzophenone | C_6H_5- | C_2H_5- | H | CH_3- | A | — | 41 |
| Methyl 1-naphthyl ketone | $1-C_{10}H_7-$ | CH_3- | H | C_4H_5- | A | 45 | 7 |
| Methyl 2-naphthyl ketone | $2-C_{10}H_7-$ | CH_3- | H | C_4H_5- | A | — | 7 |
| Isobutylacetophenone ††† | $C_{10}H_{13}-$ | CH_3- | H | C_4H_5- | A | 60-63 | 2 |
| 2,2-Dimethyl-3-(carbethoxymethyl)-cyclobutyl methyl ketone | $C_{10}H_{17}O_2-$ | CH_3- | H | C_2H_5- | A | 50 ††† | 80 |
| 2-Isopropyl-2-(carbethoxymethyl)-cyclopropyl methyl ketone | $C_{10}H_{17}O_2-$ | CH_3- | H | C_2H_5- | A | 32 ††† | 81 |

* References 60-87 are on pp. 439-440.

††† The bromo ester was used.

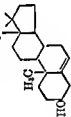
†††† The position of the isobutyl group was not stated.

††††† Forty-six per cent of the keto ester was recovered.

†††††† Twenty-five per cent of the keto ester was recovered.

TABLE I—Continued
Glycidic Esters

| Carbonyl Component | $ \begin{array}{c} \text{R}' \quad \text{O} \quad \text{R}''' \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{R}'' \quad \text{CO}_2\text{R}''' \end{array} $ Glycidic Ester Formula | | | | Con- densing Agent | Yield % | Refer- ences * |
|---|--|---------------------------------|---|---------------------------------|--------------------------|------------|-------------------|
| | R' | R'' | R''' | R''' | | | |
| 2-Undecanone | C ₁₀ H ₁₉ — | CH ₃ — | CH ₃ — | C ₂ H ₅ — | A | — | 3 |
| Benzophenone | C ₆ H ₅ — | C ₆ H ₅ — | II | C ₂ H ₅ — | A | 75, 77, 78 | 19, 40, 41, 42 |
| 2,4-Diisopropylbenzaldehydo | C ₁₂ H ₁₇ — | II | II | C ₂ H ₅ — | C | — | 46 |
| 4-(<i>p</i> -Isopropylphenyl)-2-butanone | C ₁₁ H ₁₅ — | CH ₃ — | II | C ₂ H ₅ — | C | — | 69 |
| α -Ionone | C ₁₁ H ₁₇ — | CH ₃ — | II | C ₂ H ₅ — | A | 34 | 47a, 63a |
| β -Ionone | C ₁₁ H ₁₇ — | CH ₃ — | II | C ₂ H ₅ — | A | 55, 80 | 47a, b, 63b, 82 |
| Tetrahydroionone | C ₁₁ H ₁₉ — | CH ₃ — | II | C ₂ H ₅ — | C | 73 | 69 |
| Acetone | CH ₃ — | CH ₃ — | <i>n</i> -C ₁₀ H ₂₁ — | C ₂ H ₅ — | A | 70 | 13 |
| 6,10-Dimethyl-2-undecanone | C ₁₁ H ₂₃ — | CH ₃ — | II | C ₂ H ₅ — | C | 69 | 69 |
| <i>p</i> -Methylbenzophenone | C ₇ H ₇ — | C ₆ H ₅ — | II | C ₂ H ₅ — | B | — | 42 |
| <i>p</i> -Methoxybenzophenone | C ₇ H ₇ O— | C ₆ H ₅ — | II | C ₂ H ₅ — | B | — | 42 |
| 5-(2,2,6-Trimethylcyclohexenyl)-3-pentanone | C ₁₁ H ₂₁ — | C ₂ H ₅ — | II | C ₂ H ₅ — | C | — | 69 |

| | | | | | | | |
|------------------------------------|-------------------|--|-------------------|-----------|------|---|--------|
| Dibenzyl ketone | C_7H_7- | $\begin{array}{c} \\ C_7H_7- \\ \\ H \end{array}$ | H | C_2H_5- | A | — | 83 |
| 3-Methoxy-4-benzoyloxybenzaldehyde | $C_{14}H_{13}O_2$ | $\begin{array}{c} \\ (CH_2)_5 \\ \\ H \end{array}$ | CH_3- | C_2H_5- | | — | 84 |
| Cyclohexanone | C_6H_{10} | $\begin{array}{c} \\ CH_3- \\ \\ H_2C \end{array}$ | $n-C_{10}H_{21}-$ | C_2H_5- | A | — | 13 |
| Acetophenone | C_8H_8 |  | $n-C_{10}H_{21}-$ | C_2H_5- | A | — | 13 |
| Dehydroandrosterone | | | CH_3- | C_2H_5- | A | — | 25, 85 |

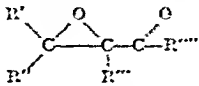
* References 50-57 are on pp. 439-440.

††† The product is an α -keto ester, not a glycidic ester.

.... The condensing agent was not mentioned. A bromo ester was used.

TABLE II
GLYCIDIC AMIDES

The procedures are similar to those used in the glycidic ester reactions. The condensing agents used are the following: A. Sodium ethoxide. B. Sodium amide. C. Sodium.

| Carbonyl Compound |  Glycidic Amide Formula | | | | Con- densing Agent | Yield % | Refer- ences * |
|----------------------|---|---------------------------------|-------------------|--|--------------------------|------------|-------------------|
| | R' | R'' | R''' | R'''' | | | |
| Acetone | CH ₃ — | CH ₃ — | H | NH ₂ — | C A | 80 55 | 24 56 |
| 3-Pentanone | C ₂ H ₅ — | C ₂ H ₅ — | H | NH ₂ — | A † B † | — — | 56 56 |
| Cyclohexanone | —(CH ₂) ₅ — | | H | NH ₂ — | — | — | 56 |
| Benzaldehyde | C ₆ H ₅ — | H | H | NH ₂ — | — | — | 56 |
| Acetone | CH ₃ — | CH ₃ — | H | N(C ₂ H ₅) ₂ — | B | 80 | 24 |
| Benzaldehyde | C ₆ H ₅ — | H | CH ₂ — | NHCH ₂ — | A ‡ | 75-80 | 24 |
| Propyl ketone | C ₃ H ₇ — | C ₃ H ₇ — | H | NH ₂ — | A | 50 | 24 |
| 1-Phenyl-2-propanone | C ₆ H ₅ — | CH ₃ — | H | NH ₂ — | — | — | 56 |
| 1-Phenyl-2-propanone | C ₆ H ₅ O— | CH ₃ — | H | NH ₂ — | — | — | 56 |
| Acetophenone | C ₆ H ₅ — | CH ₃ — | H | N(CH ₂) ₂ — | — | — | 56 |
| Cinnal | C ₆ H ₅ — | H | H | NH ₂ — | A | 70 | 24 |
| Benzaldehyde | C ₆ H ₅ — | H | H | NHC ₂ H ₅ — | A | — | 24 |

* References 50-57 are on pp. 473-479.

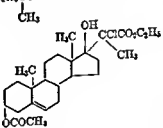
† Procedure A gave an amide m.p. 104°, procedure B, an amide m.p. 145°.

‡ The α -isocyanamide was used.

TABLE III

 α -CHLORO β -HYDROXY ESTERS

The procedure involves the addition of a mixture of ketone and α,α -dichloro ester in ether to dilute (1 to 50) magnesium amalgam. All the α -chloro β -hydroxy esters were converted in high yield to epoxy esters by treatment with alkaline reagents.

| Carbonyl Component | Product | Yield % | References * |
|-------------------------------|---|---------|--------------|
| Acetaldehyde | $\text{CH}_3\text{CHOHCHClCO}_2\text{C}_2\text{H}_5$ | 40 | 17 |
| Acetone | $(\text{CH}_3)_2\text{COHCHClCO}_2\text{C}_2\text{H}_5$ | — | 15, 16 |
| Isobutyraldehyde | $(\text{CH}_3)_2\text{CHCHOHCHClCO}_2\text{C}_2\text{H}_5$ | 68 | 17 |
| Cyclopentanone | $(\text{CH}_2)_4\text{COHCHClCO}_2\text{C}_2\text{H}_5$ | — | 17 |
| Cyclohexanone | $(\text{CH}_2)_5\text{COHCHClCO}_2\text{C}_2\text{H}_5$ | 97 | 17 |
| Benzaldehyde | $\text{C}_6\text{H}_5\text{CHOHCHClCO}_2\text{C}_2\text{H}_5$ | — | 17 |
| Heptaldehyde | $\text{CH}_3(\text{CH}_2)_5\text{CHOHCHClCO}_2\text{C}_2\text{H}_5$ | 57 | 17 |
| Acetophenone | $\text{C}_6\text{H}_5\text{COHCHClCO}_2\text{C}_2\text{H}_5$ | 95 | 16 |
| Dehydroandrosterone acetate † |  | — | 87 |

* References 60-87 are on pp. 439-440.

† This reaction failed when dehydroandrosterone was used, Ercoli and Mamoli, *Chimica e Industria*, 1937, 435.

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Numbers in bold-face type refer to experimental procedures.

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